A. M. A.
ARCHIVES OF
NEUROLOGY AND PSYCHIATRY

EDITORIAL BOARD

TRACY J. PUTNAM, Chief Editor
450 North Bedford Drive, Beverly Hills, California

HAROLD G. WOLFF, New York
STANLEY COBB, Boston
JOHN WHITEHORN, Baltimore
CHARLES D. ARING, Cincinnati
ROY R. GRINKER, Chicago
BERNARD J. ALPERS, Philadelphia
PERCIVAL BAILEY, Chicago
WILDER PENFIELD, Contributing Member, Montreal

RICHARD J. PLUNKETT, M.D., Chicago, Managing Editor

INDEX NUMBER

JUNE 1951
VOLUME 65 NUMBER 6

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

FOR THE CARE AND TREATMENT OF

MENTAL AND NERVOUS DISORDERS

• ELECTRIC SHOCK • HYPERPYREXIA •

• INSULIN •

FAIRVIEW
Sanitarium

2828 S. PRAIRIE AVE.
CHICAGO
Phone Calumet 4588

Newest Treatment for
ALCOHOLIC and NARCOTIC PATIENTS

Registered with the American Medical Association

J. DENNIS FREUND, M. D.
Medical Director and Superintendent

Appalachian Hall

An institution for rest, convalescence, the diagnosis and treatment of nervous and mental disorders, alcohol and drug habituation.

Appalachian Hall is located in Asheville, North Carolina. Asheville justly claims an unexcelled all year round climate for health and comfort. All natural curative agents are used, such as physiotherapy, occupational therapy, shock therapy, outdoor sports, horseback riding, etc. Five beautiful golf courses are available to patients. Ample facilities for classification of patients. Room single or en suite with every comfort and convenience.

For rates and further information, write

APPALACHIAN HALL
Asheville, North Carolina

M. A. Griffin, M.D.
Wm. Ray Griffin, M.D.

MILWAUKEE SANITARIUM

For Nervous Disorders

WAUWATOSA, WISCONSIN ● ***Phone:*** **Blue Mound 2600**

AT Left—
Colonial
Hall

At right—
FRANK
BILLINGS
HOUSE,
the newest
of 15 units

MAINTAINING the highest standards for more than a half century, the Milwaukee Sanitarium stands for all that is best in the care and treatment of nervous disorders. Photographs and particulars sent on request.

Two Patient
Cottage

Hospital

Illustrations show some of the 15 units in the "Cottage Plan"

Dewey
Cottage

English
Cottage

JOSEF A. KINDWALL, M.D.
CARROLL W. OSGOOD, M.D.
WILLIAM T. KRADWELL, M.D.
BENJAMIN A. RUSKIN, M.D.
LEWIS DANZIGER, M.D.
RUSSELL C. MORRISON, M.D.
ROBERT A. RICHARDS, M.D.

G. H. SCHROEDER
Business Manager

CHICAGO OFFICE—
1117 Marshall Field Annex—Wednesdays, 1-3 P.M.
—Phone CEntral 6-1162

INDEX TO

NEUROPSYCHIATRIC INSTITUTIONS SPECIAL SCHOOLS and SANITARIA

Advertising in

A.M.A. Archives of NEUROLOGY and PSYCHIATRY

Display announcements of the following institutions appear regularly in A. M. A. Archives of NEUROLOGY and PSYCHIATRY. For advertisements of those institutions which run on an every-other month basis it would be necessary to consult the advertising section of a previous or *subsequent issue.*

ADAMS HOUSE.....Boston, Jamaica Plain, Mass.
James Martin Woodall, M.D., Medical Director

ANN ARBOR SCHOOL.....1700 Broadway, Ann Arbor, Mich.
Registrar

APPALACHIAN HALL.....Asheville, N. C.
Wm. Ray Griffin, M.D.

BALDPATE, INC.....Georgetown, Mass.
G. M. Schlomer, M.D., Medical Director

BEVERLY FARM, INC.....Godfrey, Ill.
Dr. Groves B. Smith, Superintendent

BROOK HAVEN MANOR.....Stone Mountain, Ga.
Newdigate M. Owensby, M.D., Psychiatrist in Chief

BROOKLEA FARM.....Port Chester, N. Y.
George W. Henry, M.D.

CITY VIEW SANITARIUM.....Nashville, Tenn.
Will Camp, M.D., Medical Director

CLEARVIEW .....Evansville, Ind.
Dr. Albert L. Crane, Medical Director

DEVEREUX SCHOOLS.....Devon, Pa.
Helena T. Devereux, Director

FAIRVIEW SANITARIUM.....Chicago, Ill.
Dr. J. Dennis Freund, Medical Director

HIGHLAND HOSPITAL.....Asheville, N. C.
R. Charman Carroll, Medical Director

LIVERMORE SANITARIUM.....Livermore, Calif.
O. B. Jensen, M.D., Superintendent and Med. Dir.

MIAMI MEDICAL CENTER.....Miami, Fla.
P. L. Dodge, M.D.

MILWAUKEE SANITARIUM.....Wauwatosa, Wis.

NORTH SHORE HEALTH RESORT.....Winnetka, Ill.
Samuel Liebman, M.D., Medical Director

"NORWAYS" FOUNDATION, INC.....Indianapolis, Ind.
Dr. Philip B. Reed, Chief of Staff

THE MARY POGUE SCHOOL.....Wheaton, Ill.
U. S. Ayer, Manager

THE RING SANATORIUM.....Arlington, Mass.
Benjamin Simon, M.D., Director

RIVER CREST SANITARIUM.....Astoria, Queensboro, N. Y. City
and BELLE MEAD FARM COLONY.....Belle Mead, N. J.
Dr. J. J. Kindred, Founder and Consultant

CARROL TURNER SANATORIUM.....Memphis, Tenn.
Carrol C. Turner, M.D.

THE CARROL TURNER SANATORIUM

Memphis, Tenn. • Route 10, Box 288

Located on the Raleigh-La Grange Road, five miles east of the city limits. Accessible to U. S. 70 (the Bristol Highway).

FOR THE DIAGNOSIS AND TREATMENT OF MENTAL AND NERVOUS DISORDERS

53½ acres of wooded land and rolling fields. Equipment new and modern, including the latest equipment for electro-shock, physical and hydrotherapy.

Special emphasis is laid upon occupational and recreational therapy under the supervision of a trained therapist. An adequate nursing personnel gives individual attention to each patient.

The Ann Arbor School

for children with educational, emotional or speech problems

The school programs are directed by an excellent staff of teachers in special education; a speech therapist, recreational and occupational therapists and a clinical psychologist.

A training center in special education for student teachers at the University of Michigan.

Complete reports sent to referring physicians at end of each term. Licensed by the Department of Public Instruction.

Registered by the A.M.A. Member American Hospital Association.

For catalog and information address THE REGISTRAR, 1700 Broadway, Ann Arbor, Michigan

THE MARY POGUE SCHOOL

Complete facilities for training retarded and epileptic children educationally and socially. Pupils per teacher strictly limited. Excellent educational, physical and occupational therapy programs.

Recreational facilities include riding, group games, selected movies under competent supervision.

Separate buildings for boys and girls under 24 hour supervision of skilled personnel.

G. H. Marquardt, M.D. *Medical Director*

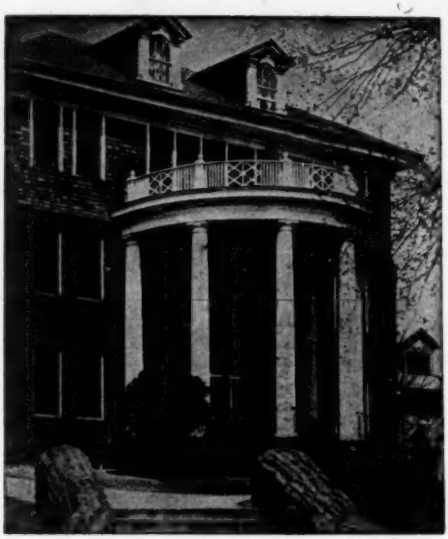
Barclay J. MacGregor *Registrar*

65 GENEVA ROAD, WHEATON, ILLINOIS

(near Chicago)

HIGHLAND HOSPITAL, INC.

FOUNDED IN 1904 **ASHEVILLE, NORTH CAROLINA**



AFFILIATED WITH DUKE UNIVERSITY

A non-profit psychiatric institution, offering modern diagnostic and treatment procedures—insulin, electroshock, psychotherapy, occupational and recreational therapy—for nervous and mental disorders.

The Hospital is located in a sixty-acre park, amid the scenic beauties of the Smoky Mountain Range of Western North Carolina, affording exceptional opportunity for physical and nervous rehabilitation.

The OUT-PATIENT CLINIC offers diagnostic services and therapeutic treatment for selected cases desiring non-resident care.

* *

R. CHARMAN CARROLL, M.D.
Diplomate in Psychiatry
Medical Director

ROBT. L. CRAIG, M.D.
Diplomate in Neurology and Psychiatry
Associate Director

Beautiful Miami Medical Center

A private hospital in a most picturesque setting. Facilities for treatment of acute medical and convalescent cases. Especially equipped for care of nervous and mental disorders, drug and alcoholic habits. Psychotherapy, Hydrotherapy, Diathermy, Insulin and Electric-Shock therapy.

MEMBER AMERICAN HOSPITAL ASSOCIATION

P. L. DODGE, M.D., *Medical Director and President*

MIAMI
MEDICAL
CENTER

1861 N. W. S. RIVER DRIVE
MIAMI, FLORIDA

CONTENTS

PAGE

Dandy's Striatal Theory of "The Center of Consciousness": Surgical Evidence and Logical Analysis Indicating Its Improbability. RUSSELL MEYERS, M.D., IOWA CITY 659

Encephalopathy Associated with Acute Diffuse Platelet Thrombosis: Report of a Case. A. HAUSER, M.D.; ALVIN BEYER JR., M.D., AND ROBERT A. BURGER, M.D., HOUSTON, TEXAS 672

Effects of ACTH on Cerebral Blood Flow and Oxygen Consumption. RALPH W. ALMAN, M.D., AND JOSEPH F. FAZEKAS, M.D., WASHINGTON, D. C. 680

Familial Occurrence of Tuberous Sclerosis. WILLARD W. DICKERSON, M.D., CARO, MICH. 683

Neurological Complications of Insulin Shock Therapy with Electroencephalographic Studies: Case Studies. LOUIS HALLE, M.D., AND J. F. ROSS, M.D. CLEVELAND 703

Babinski Reflex and Marie-Foix Flexor Withdrawal Reflex: Historical Notes. ROBERT WARTENBERG, M.D., SAN FRANCISCO 713

Glucose Tolerance in Chronic Schizophrenia and Senile States. WERNER SIMON, M.D., AND JAMES T. GARVEY, M.D., MINNEAPOLIS 717

Postpartum Necrosis of the Adenohypophysis with Hypoglycemic Convulsions. EDWARD C. CLARK, M.D.; MURRAY FRANKLIN, M.D., AND ADOLPH L. SAHS, M.D., IOWA CITY 724

EEG Prognosis in Vascular Hemiplegia Rehabilitation. CHARLES VAN BUSKIRK, M.D., AND V. R. ZARLING, M.D., MINNEAPOLIS 732

Effect of Electroshock on the Blood Pressure in Psychotic Patients. WALTER W. IGERSHEIMER, M.D., AND JAMES A. F. STEVENSON, M.D., NEW HAVEN, CONN. 740

Anticonvulsant Drug Therapy of Behavior Problem Children with Abnormal Electroencephalograms. BENJAMIN PASAMANICK, M.D., ANN ARBOR, MICH. 752

ABSTRACTS FROM CURRENT LITERATURE 767

SOCIETY TRANSACTIONS:

New York Academy of Medicine, Section of Neurology and Psychiatry, and New York Neurological Society 780

Philadelphia Neurological Society 783

NEWS AND COMMENT 787

OBITUARIES:

Lawrence Raymond Morrison, M.D. 788

BOOK REVIEWS 792

THE A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published by the American Medical Association to stimulate research in the field of diseases and disorders of the nervous system and to disseminate knowledge in this department of medicine.

Communications regarding subscriptions, reprints, etc., should be addressed, A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, American Medical Association, 535 North Dearborn Street, Chicago 10.

Manuscripts for publication should be sent to Dr. Tracy J. Putnam, Chief Editor, 450 North Bedford Drive, Beverly Hills, Calif., or to any other member of the Editorial Board. Books for review and correspondence relating to the editorial management should be sent to Dr. Putnam.

Articles are accepted for publication on condition that they are contributed solely to the A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

Matter appearing in the A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY is covered by copyright, but, as a rule, no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY or in any of the other publications issued by the Association will not be permitted.

The A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published monthly. The annual subscription price (for two volumes) is as follows: domestic, $12.00; Canadian, $12.40; foreign, $13.50, including postage. Single copies are $1.25, postpaid.

Checks, money orders and drafts should be made payable to the American Medical Association.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (three volumes): domestic, $15.00; Canadian, $16.50; foreign, $19.00. Single copies, 45 cents.

A. M. A. ARCHIVES OF INTERNAL MEDICINE—Monthly. Devoted to the publication of advanced original clinical and laboratory investigations in internal medicine. Illustrated. Annual subscription price (two volumes): domestic, $10.00; Canadian, $10.40; foreign, $11.00. Single copies, $1.00.

A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. Includes carefully prepared reviews, based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): domestic, $14.00; Canadian, $14.40; foreign, $15.50. Single copies, $1.25, except special numbers.

A. M. A. ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, annual reviews of special subjects, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original articles and general reviews in the field of pathology. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, $1.00, except special issues.

A. M. A. ARCHIVES OF INDUSTRIAL HYGIENE AND OCCUPATIONAL MEDICINE—Monthly. Devoted to the advancement of knowledge of the diseases of industry and to the publication of scientific investigation in this field. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00, including postage. Single copies, $1.00.

QUARTERLY CUMULATIVE INDEX MEDICUS—A complete subject and author index to the worth while current medical literature of the world. Issued twice a year. Volumes bound for permanent reference. Subscription price, calendar year: domestic, $20.00; Canadian, $22.00; foreign, $22.00.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street CHICAGO 10

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 65 JUNE 1951 NUMBER 6

COPYRIGHT, 1951, BY THE AMERICAN MEDICAL ASSOCIATION

DANDY'S STRIATAL THEORY OF "THE CENTER OF CONSCIOUSNESS"

Surgical Evidence and Logical Analysis Indicating Its Improbability

RUSSELL MEYERS, M.D.
IOWA CITY

DANDY [1] (1930) asserted that "the center of consciousness" in the human brain is located within the tissues irrigated by the anterior cerebral artery of the left (presumably dominant) hemisphere. This conclusion was based on his observations that after ligation of the vessel "consciousness is completely and forever lost." He asserted that a comparable result was not obtained after ligation of the anterior cerebral artery of the right (presumably subordinate) hemisphere. The concept promptly found its way into a number of textbooks of psychology, physiological psychology and psychiatry.[2]

In the same year Critchley [3] reported the results of an extensive study of syndromes following occlusion of the anterior cerebral artery and its branches. These data were not reconcilable with Dandy's reports. It was not until 1939, however, that controversial evidence derived from surgical cases similar to those constituting Dandy's material was adduced. Poppen [4] then asserted that if, during operation, measures are employed to prevent the development of a transient systemic arterial hypotension the anterior cerebral artery of either side can be ligated without altering the state of consciousness.

The correctness of Poppen's contention was acknowledged in 1946 by Dandy,[5] who then reinterpreted his previous findings and introduced additional data in support of a new theory, namely, that "the center of consciousness . . . could only be in the anterior part of the corpus striatum." He described total and permanent loss of consciousness in three surgical patients in whom the anterior portions of the

From the Division of Neurosurgery, State University of Iowa College of Medicine.

This paper was presented, with motion picture illustrations, at the Seventy-Fifth Annual Meeting of the American Neurological Association, June 12, 1950, at Atlantic City, N. J.

1. Dandy, W. E.: Changes in Our Conceptions of Localization of Certain Functions in the Brain, Am. J. Physiol. **93**:643, 1930.

2. (*a*) Hathaway, S. R.: Physiological Psychology, The Century Psychology Series, Richard M. Elliott, editor, New York, D. Appleton-Century Company, Inc., 1942. (*b*) Muncie, W.: Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior, St. Louis, C. V. Mosby Company, 1939.

3. Critchley, M.: The Anterior Cerebral Artery and Its Syndromes, Brain **53**:120-165, 1930.

4. Poppen, J. L.: Ligation of the Anterior Cerebral Artery: Its Hazards and the Means of Avoidance of Its Complications, Arch. Neurol. & Psychiat. **41**:495-503 (March) 1939; Ligation of the Left Anterior Cerebral Artery: Its Hazards and Avoidance of Complications, Surgical Practice of the Lahey Clinic, 1941, p. 691.

5. Dandy, W. E.: The Location of the Conscious Center in the Brain: The Corpus Striatum, Bull. Johns Hopkins Hosp. **79**:34-57, 1946.

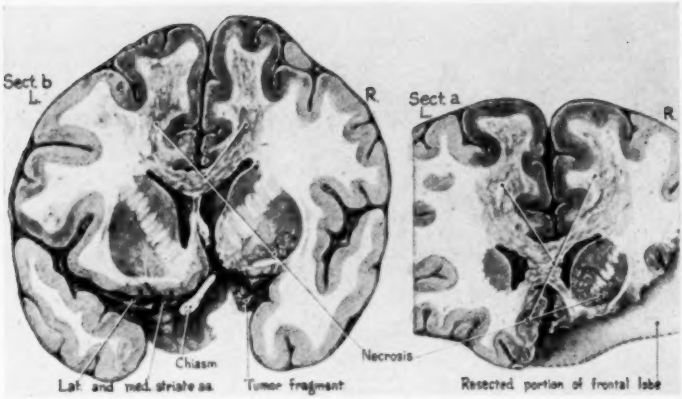


Fig. 1.—Illustration of lesions in Dandy's patient[5] (fig. 1, case 6), a woman aged 46 with a large dural meningioma. Dandy summarized the "crucial" findings as follows: "On the right (operated) side, there was necrosis of the lower half of the anterior portion of the corpus striatum . . . ; the left was intact." Note, however, extensive encephalomalacic lesions in the corpus callosum, both superior frontal lobes and the parolfactory areas.

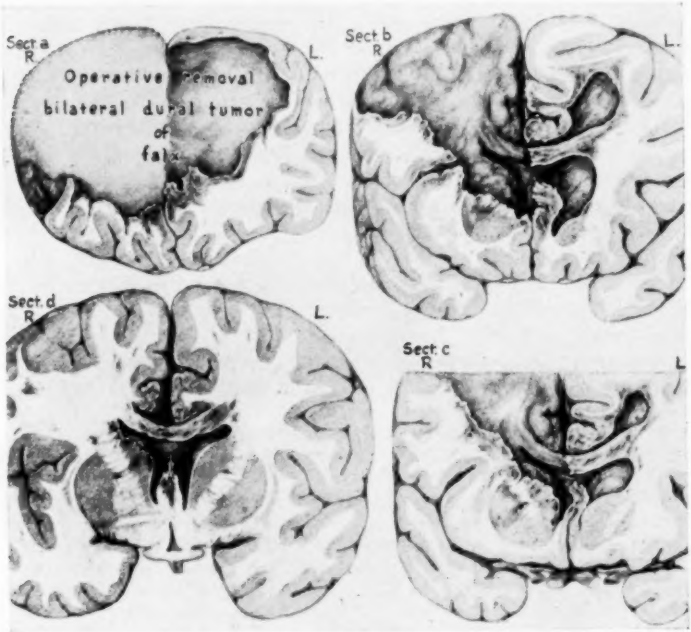


Fig. 2.—Illustration of lesions in Dandy's patient[5] (case 7), a man aged 40 with bifrontal meningioma. Summarizing the necropsy findings, Dandy stated: "The injury to the corpus striatum is shown to be at the upper anterior end of the right corpus striatum. Above the internal capsule, it has sloughed off."

Note that the striatal damage is almost entirely confined to the head of the right caudate nucleus. The anterior limb of the right internal capsule is also partly damaged. In addition to the extensive resection of frontal lobe tissue, necrosis is represented in the corpus callosum, cingulate gyrus and parolfactory region. The globus pallidus appears undamaged.

head of the right caudate nucleus and the right putamen were damaged (figs. 1 and 2) and remarked, "It is difficult to believe that a lesion of the left corpus striatum would not act similarly." He ventured the opinion that damage to the anterior striatum of either side would abolish consciousness and rejected as inconclusive the evidence adduced by other writers to support the rival cortical, thalamic and hypothalamic theories of the "center of consciousness." As with the first theory, monographs [6] embracing the new doctrine soon appeared.

Although reservation concerning the validity of Dandy's anterior striatum theory has occasionally been expressed in some circles, no empirical data have as yet been advanced to refute it.

SURGICAL EVIDENCE INCOMPATIBLE WITH THE ANTERIOR STRIATUM THEORY

Within the past decade I [7] have performed 47 operations at the level of the basal ganglia on 38 patients with Parkinsonism and two on a single patient with dystonia

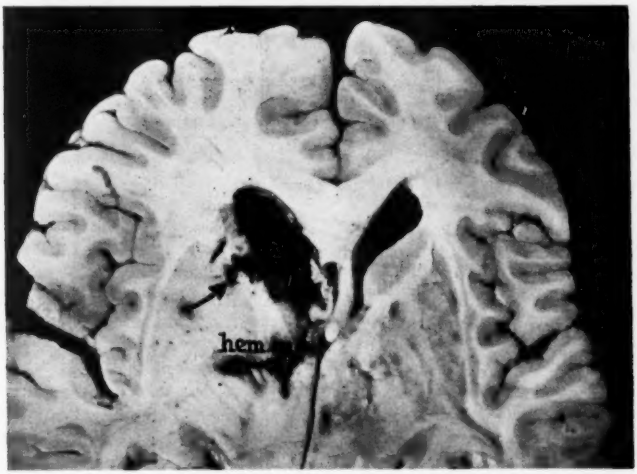


Fig. 3.—Horizontal section of brain of A. L., a housewife aged 39, with generalized rigidity and severe alternating tremors of the right side. The operative procedure planned consisted in extirpation of the head of the left caudate nucleus and section of the anterior limb of the left internal capsule. Death occurred on the third postoperative day. The figure illustrates extirpation of the head of the left caudate nucleus. The arrow points to a short segment of the curvilinear incision which cut across the anterior limb fibers. In addition, an unintended hemorrhagic extravasation (*hem.*) into the genu, thalamus and posterior pole of the globus pallidus is present. The latter probably represents the patient's fatal lesion.

musculorum, manifest mainly as spasmodic torticollis. Twenty-seven of the 39 patients were subjected to extirpation under direct vision of portions of the anterior

6. Alford, L. B.: Cerebral Localization: Outline of a Revision, Nervous and Mental Disease Monograph 77, New York, Nervous and Mental Disease Publishing Company, 1948, pp. 59-73; 80-81.

7. (*a*) Meyers, R.: The Modification of Tremors, Rigidity and Festination by Surgery of the Basal Ganglia, A. Research Nerv. & Ment. Dis. Proc. **21**:602-665, 1942; (*b*) Surgical Experiments in the Therapy of Certain Extrapyramidal Diseases: A Current Evaluation, Acta psychiat. et neurol., Supp. 67, 1951.

striatum corresponding to or exceeding the limits of the "center of consciousness," as represented in Dandy's illustrations.

Three of these 27 patients died within a few days of operation without recovering consciousness and provided postmortem confirmation of the regions intended for extirpation. One necropsy specimen is illustrated in figure 3. The remaining 24 patients recovered consciousness within two to three days after operation, usually on the first postoperative day. Of these, 14 had been subjected to extirpation on the right side, 9 on the left side and one on both sides. The various structures ablated in the entire series are indicated in the accompanying table.

The case histories of six of these patients have been reported in detail [7a] and the others summarized in a recent article.[7b] Therefore, abstracts of two representative cases only will be presented here.

REPORT OF CASES

CASE 1.—L. S., a man aged 41, a laborer, was admitted to the University Hospitals on Jan. 22, 1949, complaining of severe alternating tremors of the left upper limb of eight years' duration.

Data on Twenty-Seven Patients Subjected to Extirpation of the Anterior Striatum

Surgical Procedure *	Operative Mortality	Survival With Consciousness
Caud., Put., Gl. Pal., A.L.	..	2
Caud., Put., A.L.	1	4
Caud., Put., Pfg., A.L.	..	1
Caud., Pfg., A.L.	1	6
Caud., Pfg.	..	1
Caud. (R. and L.), A.L. (L.)	..	1
Caud., A.L.	1	8
Caud.	..	1
Total	3	24

* Caud. indicates extirpation of head of caudate nucleus; Put., extirpation of oral third or half of putamen; Gl. Pal., extirpation of oral third of globus pallidus; A.L., interruption in horizontal and vertical planes of fibers of anterior limb of internal capsule; Pfg., interruption of pallidofugal fibers; R, right side and L, left side.

He was said to have had "sleeping sickness" at the age of 16. Conventional therapy directed against Parkinsonism had proved of no value. The first operation was performed on February 2. A right superior frontal bone flap was reflected, with the use of local anesthesia, and the pallidofugal fibers were sectioned on the right side. The tremors promptly ceased but tended to return at the end of the second postoperative week. A second operation was performed on February 18. The head of the right caudate nucleus was resected; the anterior limb of the internal capsule was interrupted as far posteriorly as the genu, and the anterior half of the putamen (medial half to two thirds) was extirpated. The patient talked rationally on the second postoperative day. Since operation, he has been irregularly employed as a gardener and railroad laborer.

CASE 2.—L. Sm., a housewife and bookkeeper aged 56, was admitted to the University Hospitals on April 27, 1947, complaining of progressive rigidity of the neck and limbs, tremors of the tongue and jaw and fatigability, of four years' duration. Writing had become all but impossible. Three months prior to her admission, coarse alternating tremors appeared in the limbs of the right side. Conventional therapy against Parkinsonism had completely failed. On April 30, a left superior frontal craniotomy was performed, the left pallidofugal fibers were interrupted, the head of the caudate nucleus was extirpated and the fibers of the anterior limb of the external capsule were interrupted as far posteriorly as the genu. Though dysphasic and lethargic for several days after operation, the patient remained generally responsive. Normal responsiveness returned within a week, and shortly after returning home she resumed her usual responsibilities. She has been able to write with facility since operation.

Using similar clinical material, Browder [8] reported experiences with 13 cases of paralysis agitans in which various portions of the caudate nucleus were extirpated incidental to surgical section of the anterior limb of the internal capsule as far posteriorly as the genu. Three of the patients died after operation. Of the 10 surviving ones, all regained "consciousness."

LOGICAL ANALYSIS OF THE ANTERIOR STRIATUM THEORY

Since every scientific formulation exhibits two components—the fact finding and the hypothesizing [9]—the endeavor to evaluate Dandy's anterior striatum theory necessitates consideration of the following questions: 1: Is the problem a potentially solvable one from the scientific standpoint? 2. Are the alleged facts on which the theory is based reliable, in the sense that they were in the first place properly established? 3. Does the theory follow logically from the facts, without perceptibly violating the generally endorsed rules for the drawing of inferences? 4. Have subsequently acquired facts sustained the implicit and explicit predictions arising from the theory? These questions will be considered in order.

1. *Is the problem potentially solvable?* Every theory constitutes an attempt to answer a question, and in the instance of the anterior striatum theory the provocative question may be supposed to have taken some such form as, "Where is the cerebral center of consciousness?" Investigation properly begins here.

Students of general semantics, impressed that the form of a question goes far in determining the sort of investigation implemented and the form of the answer ultimately offered, find it expedient on being confronted with any problem to inquire

8. Browder, E. J.: Parkinsonism—Is It a Surgical Problem? New York J. Med. **47**: 2589-2592, 1947; Section of Fibers of Anterior Limb of Internal Capsule in Parkinsonism, Am. J. Surg. **75**:264-268, 1948.

9. Conventionally, the differences between fact finding and hypothesizing are regarded as qualitatively distinct and easily recognizable. A somewhat less naïve view, however, suggests that the differences are more apparent than real. Thus, concerning the psychologic process of hypothesizing, epistemologists recognize the inherence of a considerable subjective component, determined by such factors as the sensorimotor equipment of the investigator, his informational background, identifiable and nonidentifiable assumptions, prescientific and scientific prejudices, modes of imaging and habits of reasoning. Now, the most conspicuous difference between "fact" and "hypothesis" is considered to rotate around just this subjective component, for fact finding, aiming as it does at the demonstration of invariants independent of the observer, is generally believed to be characterized by "strict objectivity," a circumstance which clearly does not hold for hypothesizing. Brief reflection, however, suggests that even under the most favorable conditions a relative degree of objectivity only is attainable. "Facts" can be disclosed only by observers. Whenever the latter approach their "objects" of inquiry (i. e., their own percepts, evoked in a given situation), they invariably exercise the neurologic processes of discrimination, abstraction and generalization (Meyers, R.: The Nervous System and General Semantics: III. Perceptual Response and the Neurology of Abstraction, Rev. Gen. Semantics **6**:169-196, 1949); and in so doing they inadvertently add to, subtract from or otherwise modify those "objects." Hence, subjective processes constitute "least common denominators" of fact finding, as well as hypothesizing; and while certain measures can be adopted to minimize their more serious effects, such processes cannot by any device known at present be entirely excluded. Contrary to popular belief, therefore, "facts" share much in common with "hypotheses," and it would appear more in accord with this circumstance to envision "facts" and "hypotheses" as overlapping segments of a graded continuum, rather than as qualitatively distinct materia of science.

whether a scientifically answerable question has been asked. Johnson [10] correctly observed that merely because a sentence is composed of familiar words arranged in accord with the rules of grammatical form and terminated by a question mark does not warrant the expectation that somewhere someone can somehow furnish a proper answer. It is a cardinal principle of semantics that vague and meaningless answers only can be formulated for vague and meaningless questions.[11] Considering the terms of which it is compounded, any question that fails to specify the broad observational procedures to be used in reaching an answer must be regarded as meaningless for fruitful inquiry. In Bridgman's [12] words, some "operational principle" must inhere in it; else it constitutes a non-sense question.

With regard to the question posed above, "Where is the cerebral center of consciousness?" the investigator is obliged to examine its terms, including their hidden and manifest assumptions, with the same care as that exercised in surveying the factual data and evaluating the methods used for their acquisition.

The following assumptions are discernible in the question:

(*a*) The term "consciousness" symbolizes an unambiguous entity, susceptible of operational definition, or at least capable of being pointed at when alleged to be present, and as such constitutes a legitimate subject for scientific inquiry.

(*b*) Circumscribed anatomic brain "centers" exist within which organismic functions" reside or by which they are mediated.

(*c*) "Consciousness" is one such "function" and so is potentially localizable within some circumscribed anatomic region.

(*d*) As the use of the definite article "the" implies, one, and only one, cerebral "center" exists with which "consciousness" is related.

Logically, if any or all of these assumptions prove dubious, the validity of both the question in which they inhere and the answer reached must likewise be regarded as dubious.

With regard to the first assumption (*a*), we possess at present no generally acceptable formulation (much less an operational definition) to which the term "consciousness" refers. Some authors [13] equate the term with "awakeness," "awareness" and "self awareness"; others,[14] with "vigilance," and still others,[15] with "experience." It is doubtful whether such synonyms render the original term intelligible for purposes of scientific discourse. The most commonly proposed definitions, invariably "subjective" or "introspective," are in some instances conspicuously circular. Troland,[15b] for example, asserted that "consciousness may be defined in terms of experience as a cross section of the latter taken in time, at any moment." "Experience," on the other hand, he defines as "the sum of an infinite, continuous temporal series of consciousness." This exemplifies a "self-sealing doctrine."

Impatience with such verbal legerdemain led Watson [16] to reject the term "consciousness" as inept for purposes of psychologic study. Arguing for behaviorism, he contended that even

10. Johnson, W.: People in Quandaries, New York, Harper & Brothers, 1946, p. 53.

11. Johnson, W.: How to Ask a Question, J. Ge. Educ. **1**:113-118, 1947.

12. Bridgman, P. W.: The Logic of Modern Physics, New York, The Macmillan Company, 1932.

13. Hathaway.[2a] Stout, G. F., and Baldwin, J. M.: Dictionary of Philosophy and Psychology, New York, The Macmillan Company, 1901, vol. 1, pp. 216-217. Zilboorg, G.: Mind, Medicine and Man, New York, Harcourt Brace and Company, Inc., 1943, p. 57.

14. Delay, J.: Conscience et Diencephale, Presse méd. **55**:681-682, 1947.

15. (*a*) Muncie.[2b] (*b*) Troland, L. T.: The Principles of Psychophysiology, New York, D. Van Nostrand Company, Inc., 1929, vol. 1, pp. 89-91, 186; vol. 3, p. 54.

16. Watson, J. B.: Behaviorism, New York, W. W. Norton & Company, 1925, p. 5.

if "consciousness" does exist in the manner generally assumed, it is, and must forever remain, inaccessible to examination by every one but the subject himself. As such, it cannot be profitably employed in serious scientific study, since an indispensable requisite of scientific procedure is that every phenomenon reported on must be capable of verification by many observers. Certain later writers [17] have found it expedient to formulate "consciousness" in neobehavioristic terms, focusing attention on the discriminative and abstractive characteristics of organismic response.

The extreme futility of disputes concerning whether "consciousness" is or is not present in a given organism at a given time is well exemplified in connection with one of Dandy's patients, whose left anterior cerebral artery had been ligated and who was stated to have lain in bed with eyelids open and eyeballs moving about. Dandy regarded this patient as "completely unconscious"; Alford,[6] however, expressed doubt that he was "really unconscious." The nonpartisan observer, contemplating such disputation, is led to inquire by what conceivable operational procedures (other than behavioral) might such a controversy be settled.

"Consciousness" appears not to be an entity having identifiable existence in its own right, but to be a mere classificatory symbol that has become firmly rooted in our habitual speech and perpetuated by usage. In hospital jargon, of course, as in the idiom of the layman, it is dealt with as if it were an entity. Ayer's [18] remark, made in another context, seems pertinent here: "It is so very easy, once we have got hold of a respectable label . . . to begin to attribute a false materiality to it. . . . Those who are infected by primitive superstition that to every name a single real entity must correspond, assume that it is necessary to distinguish logically between the thing itself and any, or all, of its sensible properties."

The second assumption (*b*)—that anatomic cerebral centers exist within which "functions" reside or by which they are mediated—enjoys a wide, though largely uncritical, endorsement. According to this concept, "functions," such as language, voluntary movement, stereognosis, insight, personality, recognition of animate and inanimate objects, musical recognition, mathematical ability, respiration, blood pressure and temperature, are "controlled" by certain circumscribed anatomic regions possessing a considerable degree of physiologic autonomy.

The archetype of this notion was formulated a century and a half ago by Franz Gall,[19] founder of the first empirical doctrine of localization.[20] Gall's pupil, Spurzheim, expanded the doctrine into a system of character reading, since called phrenology. Under the later influence of Bouillaud, Dax, Broca, Jackson, Fritsch, Hitzig, Munk and Ferrier, the doctrine of localization was revised in certain of its details, especially concerning the operational events that may properly be looked on as "functions." Its essentially demonologic character, however, has always been retained and is readily recognizable in numerous current presentations.[21] A concomitant, though infrequently verbalized, assumption is that the identification of an anatomic region damage to which results in alteration of a function is tantamount to localizing that function. Hughlings Jackson long ago recognized the fallacious nature of this inference.

A considerable amount of neurophysiologic research during the past 70 years has consisted in observing how some man-conceived construct (e. g., the older "faculties" of benevolence, destructiveness, veneration, firmness and philoprogenitiveness; and the more modern "functions" of memory, gnosis, language, voluntary movement and the regulation of blood pressure) is

17. Hathaway.[2a] Hebb, D. O.: The Organization of Behavior, New York, John Wiley, & Sons, Inc., 1949, pp. 146; 217-224.

18. Ayer, A. J.: Language, Truth and Logic, ed. 2, revised, London, Victor Gollancz, Ltd., 1946.

19. Gall, F. J.: Sur les fonctions du cerveau et sur celles de chacune de ses parties, Paris, J. B. Baillière, 1825.

20. (*a*) Hollander, B.: The Mental Functions of the Brain, London, G. P. Putnam's Sons, 1901. (*b*) Solly, S.: The Human Brain, ed. 2, Philadelphia, Lea and Blanchard, 1848, pp. 256-264.

21. (*a*) Davis, L.: The Principles of Neurological Surgery, ed. 2, Philadelphia, Lea & Febiger, 1943, p. 43. (*b*) Thompson, G. N., and Nielsen, J. M.: Neuronal Patterns of the Mind (Exhibit), Tr. Am. Neurol. A. **72**:193, 1947; Area Essential to Consciousness, J. A. M. A. **137**:285 (May 15) 1948.

altered by a destructive lesion and/or stimulation of a portion of the brain.[22] That which deserves critical comment is that the evidence derived from this experimentation has been almost universally interpreted as revealing the locus of the "function" under inquiry.

To most modern students of physiology and psychology it is apparent that investigators of a century ago unwittingly committed the error of supposing that what they had abstracted from the plenum of observable behavioral processes and endowed with a name (e. g., the "faculty of benevolence") genuinely constitutes an organismic phenomenon. That much "modern" thinking partakes of precisely this oversimplifying character appears not to have often suggested itself. Clearly, a different set of man-made abstractions than those now in vogue would lead in time to the identification of corresponding brain "centers" which differ from those now depicted in our textbooks.

To suppose that the disclosure of a brain zone stimulation or destruction of which alters a given bodily activity is equivalent to spatially localizing that "function" is comparable to concluding that because manipulation of a wall switch results in the illumination or darkening of one's living room the "function" of providing light or darkness for the room must therefore be confined within the switch. There is an unfortunate tendency on the part of many writers to interpret the abolition of a "function" (blindness, paralysis, aphasia) as a simple mathematical reciprocal of the "function." Such practice is distinctly elementalistic. The evidence at present available allows one to speak of a "center" only as an anatomic region at which it is both feasible and convenient for the investigator to tap in on and modify the physiologic processes conceived of as a "function."

The third assumption (*c*)--that consciousness is a "function" of the brain, and hence theoretically capable of localization within a circumscribed portion of the organ—is but a special case of the cerebral "center" formulation dealt with above (*b*) and is vulnerable to all the criticisms developed there. It appears to have been arbitrarily adopted from among several rival assumptions without preliminary demonstration of the grounds for such preference.

The vague, subjective and often circular meanings assigned to the term "consciousness" have made it possible for generations of estimable scholars—modern, as well as ancient and medieval —to air widely disparate theories on the subject without running the smallest risk of being refuted. In general, the metaphysical doctrines of interactionism and automatism relate consciousness to the brain, whereas the doctrine of psychophysical parallelism recognizes no demonstrable causal or sequential connection between the two.[23] Beginning with Alcmaeon of Crotona (sixth century B. C.), literally millions of words have been expressed on these subjects, without resolving the pertinent issues in the smallest degree. Some writers[24] have flatly denied that "consciousness" is in any manner connected with or confined within the brain; others[25] doubt that its seat is localizable anywhere in the body or, indeed, in the material world.

---

22. Electroencephalographic, electrocorticographic, electrothalamographic and electrostriatographic technics have been added within the past two decades. Valuable as these have been, they have not provided the neurologic investigator with a new principle of attack on problems. Electrographic tracings have no physiologic meaning in themselves. They are significant only so far as they can be taken as convenient surrogates of behavioral changes. To be meaningful, they must, in the last analysis, be related to physiologic changes resulting from excitation and destruction of neural structures in such a way that they fit into the familiar scientific formula: If A, then B.

23. Strong, S.: Why the Mind Has a Body, New York, The Macmillan Company, 1903.

24. Aristotle: De partibus animalium, 652, b. 5; II (7); 656, 652 II (10); De anima III, 1, 2, Edwin Wallace, Cambridge, 1882. Exner, S.: Physiologie der Grosshirnrinde, in Hermann, L.: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, 1879, vol. II, pt. 2, p. 192. Hart, B.: The Physiology of Insanity, ed. 4, New York, The Macmillan Company, 1931, p. 35. Huxley, T. H., quoted by Thomson, W. H.: Materialism and Modern Physiology of the Nervous System, New York, G. P. Putnam's Sons, 1892, p. 104. Jackson, J. H.: On the Comparative Study of Diseases of the Nervous System, Brit. M. J. **2**:355-362 (Aug. 17) 1889.

25. Paulsen, F., cited by Hollander,[20a] p. 19. Troland.[15b]

Contrarily, a third school [26]—that to which Dandy apparently belonged—holds that consciousness must certainly reside within the brain, and a fourth,[27] while acknowledging the role played by the brain, proposes that other bodily parts (receptors, afferent nerves, muscles) probably also play important roles.

The fourth, and last, assumption (*d*)—that there is but one cerebral "center" with which "consciousness" is related—appears, like the third (*c*), wholly arbitrary. Here, again, various rival assumptions have been advocated throughout the ages, namely, that the "conscious center" is in the cerebral hemispheres,[28] the left hemisphere,[29] the cerebral cortex,[30] the frontal and prefrontal cortex,[31] the cerebrospinal fluid [32] and the diencephalon.[33] As early as 1892 Thomson [34] ventured the novel view that the cerebral hemispheres are not the sole seat of consciousness but that the basal ganglia and medulla are also involved. This notion anticipated Clark's [26g] endorsement of Penfield's [34a] recent suggestion that "all parts of the brain may well be involved in normal conscious processes, but the indispensable substratum of consciousness lies outside the cerebral cortex, probably in the diencephalon.

If, for dialectic purposes, consciousness be regarded as a genuine organismic "function," the contention that it has but one center in the brain appears particularly feeble, for those "functions" concerning which the most reliable physiologic knowledge at present exists, e. g., the regulation of blood pressure, temperature and respiration, appear each to have several corresponding "centers": neocortical, thalamicohypothalamic, bulbomesencephalic, spinal and peripheral. In consideration of this, it is unlikely that so complex a "function" as consciousness should possess but a single "center."

The difficulty of substantiating the four assumptions outlined above is usually imputed to the inherent complexity of neurologic and psychologic objects of inquiry. It is just possible, however, that the difficulty is semantic in nature; i. e., we have overlooked the circumstance that for scientific purposes "consciousness" never was anything beyond a heterogeneous group of behavioral operations, and have fallen into the delusion of supposing that because the group possesses a name it corres-

26. (*a*) Combe, G.: The Constitution of Man, ed. 2 (American), Boston, Allen and Ticknor, 1833, p. 163. (*b*) Gall.[19] (*c*) Hathaway.[2a] (*d*) Hollander.[20a] (*e*) Ladd, G. T., and Woodworth, R. S.: The Elements of Physiological Psychology, New York, Charles Scribner's Company, 1911, pp. 213; 633-685. (*f*) Morgan, C. T.: Physiological Psychology, New York, McGraw-Hill Book Company, Inc., 1943. (*g*) Ranson, S. W.: Anatomy of the Nervous System: Its Development and Function, ed. 8, S. L. Clark, editor, Philadelphia, W. B. Saunders Company, 1947, p. 312. (*h*) Solly.[20b]

27. Baldwin, J. M., and Ladd-Franklin, C.: Dictionary of Philosophy and Psychology, New York, The Macmillan Company, 1902, p. 519.

28. Combe.[26a] Solly.[20b]

29. Dandy, W. E., in Lewis, D.: A Practice of Surgery, 1933, vol. xii, pp. 45-51, Hagerstown, Md., W. F. Prior Company, Inc.; Physiological Studies Following Extirpation of the Right Hemisphere in Man, Bull. Johns Hopkins Hosp. **53**:31-51, 1933.

30. Hollander.[20a] Ladd and Woodworth.[26e]

31. Bianchi, L.: A Textbook of Psychiatry for Physicians and Students, English translation by James H. MacDonald, New York, William Wood & Company, 1906, p. 163. Troland.[15b]

32. Sömmering, cited by Hollander, [20a] p. 369.

33. Delay.[14] Thompson and Nielsen.[21b]

34. Thomson, W. H.: Materialism and Modern Physiology of the Nervous System, New York, G. P. Putnam, 1892, pp. 67; 83-86; 104-108.

34a. Penfield, W., and Gage, L.: Cerebral Localization of Epileptic Manifestations, Arch. Neurol. & Psychiat. **30**:709-727 (Oct.) 1933. Penfield, W. E.: Neuropathology of the Brain from the Problem of Mental Disorder, London, McGraw-Hill Book Company, Inc., 1934, pp. 178-183; Cerebral Cortex and Consciousness, Harvey Lect. **32**:35-69, 1937; Cerebral Cortex in Man: I. Cerebral Cortex and Consciousness, Arch. Neurol. & Psychiat. **40**:417-442 (Sept.) 1938.

ponds to a unit function the neural center for which, like some uncharted island, now only awaits discovery. From the semantic viewpoint, the question "Where is the cerebral center of consciousness?" appears as unanswerable as the questions "Where is the center of non-equilibratory coordination?" and "Where is the center of bodily economy?"

2. *Are the "facts on which the anterior striatum theory is based reliable?* In order to receive factual support, Dandy's theory requires the unambiguous demonstration that "consciousness" is totally and permanently lost whenever the anterior striatum is severely damaged, and only then. Critical inquiry into the 10 cases offered in support of this doctrine [5] reveals that the majority of the alleged facts are mere inferences and that, owing to certain errors of omission, considerable doubt attaches to the remainder. The following observations seem noteworthy:

(*a*) Six of Dandy's patients (cases 2, 3, 4, 7, 8 and 10) died within 33 hours to five days of operation, and of the remainder none lived for a sufficiently long period to warrant his unreserved conclusion that consciousness could not have been regained.

(*b*) In two instances (cases 1 and 7) the "state of consciousness" was already greatly impaired before operation, and in the clinical histories of the other eight patients a preoperative "base line" bearing on this matter was not established.

(*c*) The kind, amount, duration and complications of anesthesia, all factors capable in themselves of modifying "consciousness" during the early postoperative days, and to some extent well beyond this period, were not mentioned in the case abstracts.

(*d*) Repeated convulsions, a complication capable in its own right of introducing and maintaining a depressed "state of consciousness," were exhibited by five patients (cases 2, 3, 7, 8 and 9).

(*e*) No criteria by which the condition of "complete unconsciousness" might be determined were laid down. Lacking such, the reader is obliged to rely entirely on the author's description of his patient's behavior. In at least three instances (cases 5, 7 and 10) the patients exhibited during the postoperative period movements characterized by more or less adaptation. The use of the term "completely unconscious" in such connections is manifestly challengeable.

(*f*) Nine of Dandy's 10 subjects harbored brain tumors. Inasmuch as cerebral neoplasms are notorious for their capacity to produce widespread, and sometimes remote, disturbances in electrical discharges and circulation of the blood and cerebrospinal fluid, most investigators consider it ill advised to draw on such material in the endeavor to localize physiologic and psychologic processes.

(*g*) In seven instances (cases 1, 2, 3, 4, 5, 8 and 9) no lesions of the striatum were demonstrated. They had not been searched for at the time of necropsy, and during the subsequent years the specimens had been lost or discarded. Dandy merely inferred from the circumstance of "unconsciousness" during life that striatal lesions must have been present. He then employed these cases to support his generalization that lesions of the striatum result in unconsciousness. This procedure exemplifies the fallacy known in logic as *petitio principii*.

(*h*) Of the three protocols (cases 6, 7 and 10) regarded by Dandy as furnishing crucial evidence in support of his theory, each presents, in addition to lesions of the anterior striatum, extensive areas of necrosis of the parolfactory cortex, the rostrum and genu of the corpus callosum, the cingulum, the superior frontal gyrus and various neighboring structures. These areas were summarily discounted as bearing on the problem of "unconsciousness."

3. *Does the theory follow logically from the facts?* Dandy's theory holds that there is but one "center of consciousness"—that located in the anterior striatum. The *modus operandi* by which this inference was reached exhibits two aspects: (*a*) the negative, in which all rival propositions were excluded, and (*b*) the positive, in which the anterior striatum was identified.

(*a*) The negative aspect is exemplified in Dandy's words as follows:

. . . One can be certain that neither cerebral hemisphere above the basal ganglia plays any part in consciousness. This statement is based upon seven total *right* hemisphere removals that I have performed in man, another by Gardner and the single total removal of the *left* cerebral hemisphere by Zollinger . . . [after which] no appreciable disturbance of mentality results. There can, therefore, be no doubt that consciousness is not related to the cerebral hemispheres; it must, therefore, be referred to the basal ganglia or thalamus, or possibly the hypothalamus or brain stem.[5]

By a similar line of reasoning, Dandy dismissed the alternative propositions that the thalamus, hypothalamus and/or brain stem might play a responsible role. The dubious process of piecemeal elimination is in evidence here. Evidently, the author was either oblivious of or felt under no obligation to repudiate Thomson's [34] suggestion that consciousness can use one or the other or both hemispheres and/or deep-lying agents, Lashley's [35] extensive researches in the higher psychologic processes which lent support to the plausible concepts of "mass functioning" and "equipotentiality," Jefferson's [36] clinical studies in confirmation of Lashley and pertinent clinical and experimental findings in human anencephalic monsters. His conclusion, therefore, exemplifies a logical *non sequitur*.[37]

(*b*) The cerebral cortex having been thus disposed of, Dandy undertook to establish the positive aspect of his thesis. Citing the autopsy findings, he directed attention to necrosis of the anterior portion of the corpus striatum demonstrable in three cases (6, 7 and 10). In two of these the lesions in the basal ganglia were confined to the head of the caudate nucleus and the putamen of the right side, from which circumstance he concluded that "bilateral involvement is not necessary" for the production of "unconsciousness." Furthermore, from the fact that the lesions in each case were "far removed" from the hypothalamus, Dandy completely dismissed the possibility that the latter might play a role in "consciousness."

There is [he contended] only one part of the brain that could meet this condition, i. e., the corpus striatum. . . . The center of consciousness is, therefore, the "integrator" of all the voluntary activities of the brain. With the loss of this center the body becomes a vegetative organism.

35. Lashley, K. S.: Brain Mechanisms and Intelligence, Chicago, University of Chicago Press, 1929.

36. Jefferson, G.: Removal of Right or Left Frontal Lobes in Man, Brit. M. J. **2**:199-206, 1937.

37. In reviewing the steps by which Dandy was led in 1930 [1] to conclude that the "center of consciousness" lies within the tissues irrigated by the left anterior cerebral artery, the critical investigator discovers the same fallacy as that to which attention is drawn above. "It has been found," Dandy asserted, "that after ligation of the anterior cerebral artery on the left side consciousness is completely and forever lost. This does not result when the same vessel is ligated on the right side. There is, therefore, within the limits of the distribution of this vessel an area specifically concerned with consciousness. . . . The same result follows when this vessel is occluded at the middle of the corpus callosum, indicating that the seat of consciousness is posterior to this point in the vessel. . . . Since the entire body of the corpus callosum may be split in the middle without any appreciable disturbance of function, this structure is eliminated from participating in the important functions which hitherto have been ascribed to it." That not all possible variables had been entertained by Dandy in reaching this conclusion was convincingly demonstrated within a decade by Poppen,[4] who reported seven cases in which the left anterior cerebral artery and three in which both anterior cerebral arteries had been ligated without abolishing "consciousness."

An unbiased review of these cases, however, reveals in each instance a logical *non sequitur*: Patient 7 survived but 33 hours, and patient 10, 48 hours, after operation—periods far too short to permit the conclusion that the "unconsciousness" asserted to have been present must have been enduring. Furthermore, in each of these patients certain adaptive movements were observed during the postoperative period, a circumstance which introduces some question as to the alleged completeness of the loss of consciousness.

That an extended period of the condition clinically regarded as "unconsciousness" does not as such warrant prognostication of permanent loss of consciousness is pointed up by the case of P. McC., a girl aged 10 years, recently under my care. After an automobile injury she exhibited signs of "decerebration" for 11 days and "regained consciousness" only on the fifty-ninth day. It is now 1½ years since injury. The patient has meanwhile resumed school work and on several occasions has obtained grades of A and 100. The main residues of her injury consist of fatigability and amimia in laughing and crying.

Again, one patient (case 7) was described as having been "semiconscious and unresponsive to questions" prior to operation. The protocol in this case provides no reason for supposing that a lesion of the striatum existed preoperatively. In view of this, it is difficult to see why the postoperative depression must have been due, as Dandy argued, to the striatal lesion alone, particularly since the last 12 hours of the patient's life were marked by recurring convulsions. A similar equivocating factor obtained for the other patient (case 10), whose condition toward the end of the first postoperative day necessitated reexploration for a possible postoperative blood clot. No clot was found, but a "slight" degree of increased intracranial tension, manifest as bulging of the brain, was encountered. Dandy apparently considered this inconsequential to the patient's "unconsciousness."

Finally, as noted above, the gross brain sections in cases 6, 7 and 10 were characterized by extensive damage beyond the striatum. In this connection, therefore, two serious fallacies are detectable: that of imputing to one agent what may in fact be ascribable to others, and that of assuming that because one agent plays thus and such a role, another cannot or does not.

4. *Have subsequently disclosed facts sustained the predictions that arise from the theory?* Scientific method recognizes but one criterion by which the validity of any theory may be sustained, that of predictability. One implied prediction of Dandy's theory is that a destructive lesion of the anterior striatum of one or both sides will regularly be followed by complete and permanent unconsciousness. This prediction has not been borne out in either of the two pertinent series of cases thus far reported by Browder [6] and me.[7]

COMMENT

The *modus operandi* by which the anterior striatum theory was formulated is neither unique nor rare. On the contrary, it is only slightly less frequently encountered in medical discourse than in lay literature. With but minor alterations, the critique outlined above might with propriety be applied to hundreds of articles published each year. All this points up the important lesson that the structure of medical science depends quite as much on knowledge of and conformance to the principles of logic, general semantics and scientific method as on comprehension of the embryology of the heart and the metabolism of iodine.

Ordinarily, no obligation rests on the critic to propose a substitute for a rejected formulation. In the present instance, however, a substitute possessing the scientific merit of being amenable to operational inquiry happens to be available. The symbols "consciousness," "unconsciousness" and "center" of thus and such a "function," for which no verifiable referents exist, are discarded, and a set of "norms" accurately describing the observable responses of the organism to a variety of conveniently reproducible stimuli—nocuous, tactile, auditory, verbal, social, etc.—is compiled. The "norms" will, of course, vary for different species and, depending on age, degree of maturation, cultural habits, etc., for individuals within a species. With such data at hand, it becomes a relatively simple matter to ascertain, through the technics provided by neuropathology, physiology and psychology, all regions of the brain which on being stimulated or damaged result in some modification of the cataloged responses. One then speaks of brain regions the integrity of which is more or less required for the integrity of a particular response.

The various responses may now be compared, singly and in combination, and whenever agreement is reached by qualified observers that two or more responses vary consistently on stimulation or damage of a particular brain region, some convenient symbol is assigned to the complex. Similarly, whenever two or more brain regions appear to be consistently related to a particular response or constellation of responses, a convenient symbol is assigned. In this way, every symbol in the language of neurology stands for a verifiable referent, and the latter can be demonstrated whenever occasion demands by employing its proper operational device. Whether the term "function" is then retained in the idiom of science becomes a mere matter for linguistic agreement among investigators. If retained, its meaning must, of necessity, differ from that currently in use.

SUMMARY AND CONCLUSIONS

In 1946 Dandy marshaled evidence to support the theory that the cerebral "center of consciousness" is located in the anterior striatum—specifically, in the oral portions of the head of the caudate nucleus and the putamen. He maintained that a lesion of these structures on one or both sides is followed by complete and permanent loss of consciousness.

Of 38 patients with Parkinsonism and 5 with torticollis on whom I operated within the past decade, 27 were subjected to removal, under direct vision, of portions of the anterior striatum corresponding to or exceeding the limits of the "center" described by Dandy. Three of the 27 patients died after operation and necropsy confirmed the existence of the intended lesions. Of the remaining 24 patients the postoperative period of none was characterized by enduring "unconsciousness." In 14 instances the surgical lesions were produced on the right side; in 9, on the left, and in one, on both sides.

An analysis of the factual data presented by Dandy and the *modus operandi* by which he formulated the anterior striatum theory suggests that (*a*) in its present form the problem is not scientifically solvable; (*b*) the clinical material employed was inept for its intended purposes; (*c*) inferences were commonly mistaken for facts; (*d*) unwarranted assumptions were frequently made; (*e*) numerous variables inhering in the problem were overlooked or arbitrarily discounted, and (*f*) the fallacies of *petitio principii* and *non sequitur* were exercised.

The currently available data render the anterior striatum theory of the "center of consciousness" improbable.

ENCEPHALOPATHY ASSOCIATED WITH ACUTE DIFFUSE PLATELET THROMBOSIS

Report of a Case

A. HAUSER, M.D.
ALVIN BEYER Jr., M.D.
AND
ROBERT A. BURGER, M.D.
HOUSTON, TEXAS

CLINICAL and pathological involvement of the central nervous system has been noted as a prominent feature of acute diffuse platelet thrombosis (disseminated arteriolar and capillary platelet thrombosis; thrombotic thrombocytopenic purpura; acute thrombocytopenic purpura; thrombocytic acroangiothrombosis), which was first described by Moschcowitz[1] in 1925 and established as a disease entity by Baehr, Klemperer and Schifrin[2] in 1936. This is a rare disease, and only 23 cases have been reported. Only one of these reports has appeared in a neuropsychiatric journal,[3] and the condition has not been mentioned in any of the modern textbooks of neuropathology, neurology or psychiatry. With this in view, we report this additional case of a disease which has been delineated rather extensively from the pathological standpoint, in order to emphasize the clinical, neurologic and psychiatric aspects. Since antemortem diagnosis of the disease has been reported only in one instance, it is felt that neuropsychiatrists should become more familiar with the clinical picture, so that it will be considered in the differential diagnosis of every case of encephalopathy of sudden onset.

CLINICAL FEATURES

This disease, of unknown etiology, has occurred in persons of either sex, white or colored, the ages ranging from 9 to 66 years. The onset is acute and insidious, and after a variable progressive course every case thus far reported

---

Read before the Missouri Neuropsychiatric Society, Oct. 11, 1950, in St. Louis.

This case is reported with permission of the family physician, Dr. Thomas P. Kennerly, Houston, Texas.

From the Department of Neuropsychiatry, Baylor University College of Medicine, and the Pathology Section of the Memorial Hospital.

1. Moschcowitz, E.: An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries: An Undescribed Disease, Arch. Int. Med. **36**:89-93 (July) 1925.

2. Baehr, G.; Klemperer, P., and Schifrin, A.: An Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thromboses of Capillaries and Arterioles, Tr. A. Am. Physicians **51**:43-58, 1936.

3. Adams, R. D.; Cammermeyer, J., and Fitzgerald, P. J.: Neuropathological Aspects of Thrombocytic Acroangiothrombosis: Clinico-Anatomical Study of Generalized Platelet Thrombosis, J. Neurol., Neurosurg. & Psychiat. **11**:27-43 (Feb.) 1948.

has terminated in death. The duration of the terminal illness varied from one week to two months. Clinical features include, predominantly, vague nonlocalizing symptoms; fever, purpura, anemia and thrombocytopenia, and baffling mental and neurologic signs. Mild icterus was present in about 50 per cent of the cases, including our own. This sign, associated with the profound deterioration of the patient, resembles the clinical picture observed in some of the fatal cases of infectious hepatitis. The mental and neurologic symptoms, which are vague and nonlocalizing, may wax and wane as the disease rapidly progresses but invariably become the prominent feature of the disease before the patient dies.

NEUROLOGIC AND MENTAL SYMPTOMS

Among the neurologic and mental symptoms are headache, local and generalized paresthesias, paresis of extremities, facial paresis, hemiplegia, muscular weakness, Kernig's sign, dysphagia, apraxia, aphasia, clonic muscular twitchings, convulsions (rare), vertigo, restlessness, drowsiness, lethargy, irritability, whining, moaning, confusion, delirium, stupor and coma. The symptoms may be fleeting and transient, although ultimately there is progression to delirium, stupor and coma before the patient dies. Widespread occluding platelet thrombi in the cerebral arterioles and capillaries, involving the cerebral cortex, basal ganglia, brain stem nuclei and cerebellum, account for the bizarre clinical symptoms, best described by the term encephalopathy. Our case ran true to form and did not differ in any particular aspects from those previously reported. Without postmortem examination, however, the disease process would not have been correctly diagnosed, since disseminated platelet thrombosis was not considered in the differential diagnosis by the various clinicians, including a general practitioner, an internist, a thoracic surgeon, an ophthalmologist and a neuropsychiatrist.

REPORT OF CASE

History.—Mrs. B. L., aged 20, white, a housewife, was admitted to Memorial Hospital, Houston, Texas, on April 9, 1950, with complaints of headache, malaise and fatigue. She had apparently been well until March 17, three weeks before her admission, when her husband noticed loss of weight, which was associated with and preceded by loss of appetite. In addition, there was known anemia, and a mild painless jaundice had been present several weeks before her admission. There was a history of clay-colored stools, but this symptom had not been noted recently. The patient was said to be under mental strain, due to worry over a lawsuit and domestic situations. She was nulliparous. Her only known past illness was measles, occurring in childhood. There was no history of cancer, tuberculosis or diabetes. In February 1945, at the age of 15, the patient was treated at Memorial Hospital for an acute uncomplicated pelvic infection, diagnosed as "acute salpingitis." It was noted in the history that she was emotionally unstable on this admission, and she was discharged as improved after four days in the hospital. Medication included administration of 400,000 units of penicillin and approximately 7 Gm. of sulfathiazole. The family history was noncontributory. The parents and sisters were living and well.

Course in the Hospital.—On her admission into the hospital, on April 9, the patient was ambulatory and mentally alert, and the physical status was within normal limits except for mild jaundice. The temperature was 100 F.; the blood pressure, 110/60; the weight, 112½ pounds (51.1 Kg.); the height, 5 feet 7 inches (170 cm.). During the first five days in the hospital complaints recorded included headache, nausea and vomiting. On April 14, thoracic consultation was obtained because a roentgenogram of the chest at this time showed a small circumscribed

opacity at the upper portion of the lower lobe of the right lung. There was a history of vague pleuritic pains for the past two or three years. The consultant suggested the following diagnoses, in this order: tuberculosis, coccidiomycosis and a primary malignant growth in the lung.

On April 17 the patient was restless, moaning, confused and semicomatose. At night she became uncooperative and noisy and had to be restrained with bed sheets. By the next day, April 18, although there was motor restlessness with muscular twitching, she was rational and in good spirits, laughing and talking. She complained of numbness in the left arm. Neurologic and psychiatric consultation was completed on April 19. The reflexes, sensory status, motor status and cranial nerves were normal. The patient responded normally to all questions, was clear mentally, seemed well oriented and appeared to be in a fairly good humor. There was no abnormal ideation. There was continuous whining during the examination. The husband stated

Fig. 1.—Partial occlusion of a vascular lumen (heart) by a platelet thrombus. Hematoxylin and eosin stain; × 450.

that she was inclined to whine, and he considered that this was normal for the patient. She complained of abdominal discomfort; the abdomen was slightly distended, and there was mild scleral jaundice.

On April 20 the medical consultant noted that there had been spiking temperature over a period of two to three days and disorientation. Physical examination at this time revealed that she was well nourished, with no apparent jaundice. There were evidence of dehydration and large ecchymoses over the trunk and thighs. The blood pressure was 120/80. There were numerous rhonchi in the lungs; the heart rate and rhythm were regular, and no murmurs were heard. The abdomen was tense. There was suggestion of spasm in the upper part of the abdomen. Peristalsis was present. The liver and spleen were not palpable. The diagnosis of acute infec-

tious hepatitis was considered. The nurses' notes described the patient as lethargic, uncooperative, crying, whining, disoriented and irrational during the 24 hour period. The temperature (rectal) rose to a peak of 103 F.

On April 21, the temperature reached 104 F., her condition was worse and she was in a comatose state. By April 22 she was obviously moribund. On this date bleeding developed from all orifices. Seventy-two milligrams of menadione was given intravenously. The bleeding gradually ceased. Treatment up to and including this time had included administration of penicillin and chloramphenicol, multiple blood transfusions, tube feedings, vitamin therapy and oxygen inhalations. On April 22 there was apparent jaundice again. On April 24 there was evidence of consolidation of the lower lobe of the right lung. The patient died April 25, on the sixteenth hospital day.

Laboratory Data.—The blood count on admission showed 2,180,000 red cells, 7 Gm. of hemoglobin and 7,300 white cells, with a differential count of 14 stab forms, 65 polymorphonuclear leukocytes and 21 lymphocytes. There were marked poikilocytosis, anisocytosis and polychromatophilia. The urine was acid, with a specific gravity of 1.015, a negative reaction for albumin and sugar and no microscopic constituents. On April 10 the urine gave a positive reaction for urobilinogen in a dilution of 1 : 80. Several repeated blood counts showed a status similar to that on admission. The red blood cell count varied from 2,000,000 to 2,700,000. Serologic tests of the blood for syphilis gave negative reactions. On April 17 the fasting blood sugar was 140 mg. per 100 cc., and the icteric index, 15.8. Examination of the sputum on April 15 revealed no acid-fast bacilli or fungi; there were a few gram-negative bacilli. On April 19 the differential count showed 19 stab forms, 65 polymorphonuclear leukocytes, 12 lymphocytes and 4 monocytes. Two normoblasts were seen per 100 leukocytes, and no thrombocytes were noted on the slide. There were anisocytosis and poikilocytosis. On April 21 the serum amylase was 40 units (40 mg. glucose per 100 cc.). There were 2,790,000 red blood cells, 8.50 Gm. of hemoglobin per 100 cc., 120,000 thrombocytes and 0.8 per cent reticulocytes. On April 22 agglutination tests for typhoid, paratyphoid, brucellosis and typhus gave negative results. Examination of the spinal fluid on April 19 showed 45 mg. of protein per 100 cc., no globulin, no cells, a negative Wassermann reaction and a colloidal gold curve of 00000. The Widal and Weil-Felix reactions were negative. On April 24, the nonprotein nitrogen of the blood was 42.5 mg., the urea 30 mg. and the bilirubin 7.8 mg., per 100 cc.; the van den Bergh test gave a normal reading. The cephalin flocculation test gave a negative result. A blood culture taken on April 21 was reported to be sterile.

Autopsy.—Gross Examination: The skin showed many small petechiae and ecchymoses, particularly on the flanks and thighs. There was a large ecchymosis in the scalp. The pericardial cavity contained 45 cc. of slightly opaque, yellow fluid, in which strands of fibrin floated. There was some roughening of the visceral pericardium. The left pleural cavity contained 100 cc. of serosanguineous fluid. No fluid was found in the right pleural cavity. There was a general yellow pigmentation of the viscera and connective tissues.

The heart weighed 300 Gm. The musculature was pale, and many petechiae were scattered through the pericardium, myocardium and in a subendocardial location. The valves were normal.

In the right lung there was a well demarcated nodule, with a caseous necrotic center and fibrous wall. In the esophagus, near the cardia, three linear hemorrhagic areas involved the mucosa. Petechiae were scattered throughout the serosal surfaces of the small and large intestines.

Each kidney weighed 185 Gm. The cortical surfaces showed numerous petechiae. Ecchymoses were noted beneath the mucosa of the pelves and major calices.

The brain weighed 1,380 Gm. With the exception of small areas of congestion, no other gross changes were noted in the cerebral cortex, basal ganglia, midbrain, pons, cerebellum or brain stem. Some hemorrhage was noted in the sphenoid sinus.

Microscopic Examination: Sections of the myocardium showed a large area of hemorrhage. Many small endothelium-lined vascular channels showed partial to complete occlusion by small granular, pale-staining thrombi (fig. 1). The lesions were variable in size, and in the smaller lesions there was deposition of eosinophilic-staining material in a subendothelial location. The intima over the deposits was intact. In many of the lesions the thrombus was covered by proliferated endothelial cells. Occasional vessels showed almost complete occlusion by the thrombi. The myocardial fibers were intact, and the sarcoplasm appeared granular.

In sections of lungs, the alveoli showed many polymorphonuclear leukocytes and some pigment-containing phagocytic cells. The nodule in the right lung, described above, showed a caseous necrotic center, well demarcated from the adjacent lung parenchyma by a layer of fibrous tissue, which appeared hyalinized.

The liver showed only some swelling of the parenchymal cells, with a loose granular cytoplasm. Some of these cells contained small amounts of granular yellow-brown pigment. The spleen showed some congestion. No specific vascular changes were noted.

The pancreatic arterioles contained many hyaline thromboses, a large number being almost completely occluded. Some of the vascular channels in the islets of Langerhans showed thrombi, as described above.

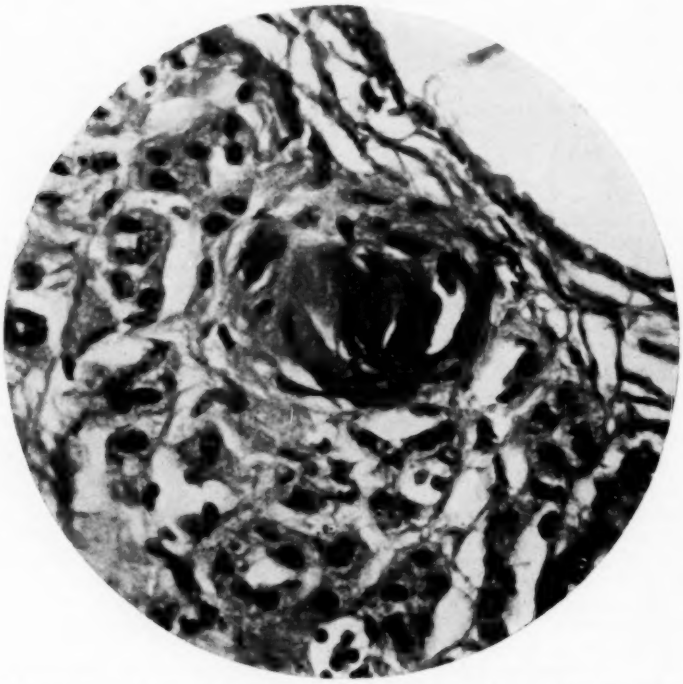


Fig. 2.—A more advanced lesion in the adrenal gland. The thrombus shows an intact covering of endothelium. Hematoxylin and eosin stain; × 450.

In the superficial cortex of the adrenal glands, hyaline thrombi were noted in the capillaries and arterioles (fig. 2). A few small areas of hemorrhage were noted in the glands, particularly in the cortex.

Sections of the esophagus showed ulceration of the mucosa with large areas of submucosal hemorrhage.

In the kidneys, areas of hemorrhage were noted beneath the epithelium of the pelvis and in the cortex and medulla. In some areas the hemorrhage was perivascular. A few small endothelium-lined vascular channels contained hyaline thrombi.

Sections of vertebral bone marrow showed hyperplasia and an apparent increase in the number of megakaryocytes. Thromboses were noted in the arterioles and capillaries of the pituitary gland.

In sections of the brain, small endothelium-lined vascular channels containing thrombi, as described above, were observed in small numbers, particularly in the cerebral cortex (fig. 3). The cerebral cortex showed mild dilatation of the perivascular and perineuronal spaces. Congestion was prominent, particularly in the subcortical white matter. Sections of the basal ganglia, brain stem and cerebellum showed some congestion.

The anatomic diagnoses were disseminated arteriolar and capillary platelet thrombosis, bronchopneumonia and ulceration of the esophagus.

RÉSUMÉ OF CLINICAL PICTURE

According to Wyatt and Lee,[4] who summarized 22 cases, the sudden development of an encephalopathy, with severe anemia, low thrombocyte count and persistent fever, suggests this unique disorder. All the patients were acutely ill and unusually pale and icteric. Petechiae and ecchymoses were noted over the body surfaces. Neurologic changes occurred in the form of either mental confusion, stupor, coma and convulsions, or, on occasion, baffling lateralizing signs. In laboratory studies the urine was frequently found to contain blood cells and increased urobilinogen, but no bile. Cardinal features of the hematologic studies

Fig. 3.—Vascular lesion of diffuse platelet thrombosis (brain). Hematoxylin and eosin stain; × 450.

4. Wyatt, J. P., and Lee, R. S.: Hemorrhagic Encephalopathy Due to Disseminated Thrombocytic Thrombosis: Report of a Case, Arch. Path. **49**:582-589 (May) 1950.

were profound anemia and pronounced thrombocytopenia. In the majority of the reported cases all these features appeared at some time during the course of the fatal illness, but the complexity of the clinical picture rendered antemortem diagnosis difficult.

The clinical and pathological aspects of this disease have been well described in the literature, especially in the journals of pathology. Although only 23 cases have been reported, it is probable that many more have occurred since the first report, in 1925, and have either not been recognized or, if recognized, not been published. There are no pathognomonic clinical or laboratory signs. A variety of nonlocalizing neurologic and confusing mental symptoms, which may change as the disease progresses, occur in nearly every case. Thus, if the vague clinical picture associated with anemia, thrombocytopenia and jaundice can be focused on the diagnostic horizon whenever the neurologist or psychiatrist is confronted with an encephalopathy of undetermined origin, the diagnosis of acute platelet thrombosis becomes a possibility. The widespread disseminated vascular platelet thromboses in the brain are consistent with the clinical picture of encephalopathy that occurs repeatedly with the syndrome of acute diffuse platelet thrombosis.

In the most recent case, the twenty-third, reported by Goldenberg, Thayer and Hastings [5] the patient, aged 23, was first believed to have a major psychosis and consequently was placed in a psychiatric hospital. Diagnosis was made only post mortem. How many other deaths from similar acute neurologic and psychiatric illnesses of unexplained origin can be attributed to this disorder?

From the neuropsychiatric standpoint, the differential diagnosis would involve the ruling out of atypical encephalitis, brain tumor and the various types of hemorrhagic encephalopathy. In our case, infectious hepatitis was the first choice in diagnosis before death. Other diseases which have been considered in the differential diagnosis include lupus erythematosus, purpura hemorrhagica and periarteritis nodosa.

ETIOLOGY

A hypersensitivity state has been suggested as the etiologic factor in disseminated platelet thrombosis. The evidence was discussed by Gore [6] in reviewing some of the reported cases. Sensitivity to sulfonamide drugs occurred in two cases.[7] Another patient [7a] had "hives" for one year, requiring administration of antihistaminic drugs. Diffuse proliferative glomerulitis [8] and subacute glomerulo-

5. Goldenberg, P. T.; Thayer, J. E., and Hastings, L. P.: Febrile Thrombopenic Purpura with Hemolytic Anemia and Platelet Thrombosis, New England J. Med. **243**:252-256 (Aug. 17) 1950.

6. Gore, I.: Disseminated Arteriolar and Capillary Platelet Thrombosis, Am. J. Path. **26**:155-167 (Jan.) 1950.

7. (*a*) Fitzgerald, P. J.; Auerbach, O., and Frame, E.: Thrombocytic Acroangiothrombosis (Platelet Thrombosis of the Capillaries, Arterioles, and Venules), Blood **2**:519-541 (Nov.) 1947. (*b*) Engel, G. L.; Scheinker, I. M., and Humphrey, D. C.: Acute Febrile Anemia and Thrombocytopenic Purpura with Vasothromboses, Ann. Int. Med. **26**:919-933 (June) 1947.

8. Muirhead, E. E.; Crass, G., and Hill, J. M.: Diffuse Platelet Thromboses with Thrombocytopenia and Hemolytic Anemia (Thrombotic Thrombocytopenic Purpura), Am. J. Clin. Path. **18**:523-532 (July) 1948.

nephritis,[6] which are thought to be the result of hypersensitivity, were present in other cases. Acquired hemolytic anemia,[9] which may be a manifestation of sensitization, was mentioned in three cases. In our case there was no history of any type of sensitivity to drugs or other substances. An abnormal clotting mechanism of the circulating blood has also been advanced in connection with the etiology, though there is scant proof for this theory. Finally, the evidence for an association with the collagen diseases has been considered but appears inconclusive at this time.

TREATMENT

In all cases thus far reported treatment has been unsuccessful and the patient has died. However, Moschcowitz [1] stated that Dr. Max Lederer, of Brooklyn, reported that in four cases, clinically identical, all the patients had recovered after a single blood transfusion. All other investigators who have tried blood transfusions, usually repeated, have failed to arrest the rapid progress of the disease; so it appears unlikely that Lederer's cases represented the same disease. In 1947 Engel, Scheinker and Humphrey [7b] reported the only case in which an antemortem diagnosis was made correctly. This case, of a Negro girl aged 15, also is the only one reported in which the patient showed sufficient improvement to leave the hospital after treatment, which in this case consisted of five blood transfusions, intravenous administration of fluid and use of various sulfonamide drugs, for what was thought to be a sepsis. She returned to the hospital in relapse a month later. At that time, because no platelets were found, a splenectomy was done, and the patient died. In two other cases, a splenectomy was done because of the low platelet count, and both the patients died. Singer, Bornstein and Wile,[10] in 1947, raised the question of the use of bishydroxycoumarin U.S.P. (dicumarol®) and heparin, but no cases in which these anticoagulants were used have been reported. Our knowledge of this condition is based on fatal cases; perhaps milder cases, in which the patient recovers, exist but are unreported and therefore unknown.

Since the cause has not been determined, treatment remains chiefly on a supportive basis and cannot be directed toward causative factors. One can only hope that in the future the diagnosis can be made ante mortem, so that various approaches to treatment may be attempted.

SUMMARY

Another case of acute diffuse (generalized) platelet thrombosis with autopsy is reported. This is the twenty-fourth case to be reported in the literature.

The clinical, neurologic and psychiatric aspects of the disease are emphasized in order to call attention to the need for further consideration of this unusual disease by neuropsychiatrists in the differential diagnosis of acute encephalopathies.

The lack of fundamental knowledge concerning the etiology and treatment of this disorder is discussed.

Dr. Ira Gore, Hermann Hospital, Houston, Texas, prepared the special stains and correlated this case with those he recently published from the files of the Army Institute of Pathology.

9. Adams, Cammermeyer and Fitzgerald.[3] Engel, Scheinker and Humphrey.[7b] Trobaugh, F. E., Jr.; Markowitz, M.; Davidson, C. S., and Crowley, W. F.: An Acute Febrile Illness Characterized by Thrombopenic Purpura, Hemolytic Anemia and Generalized Platelet Thrombosis, Arch. Path. **41**:327-334 (March) 1946.

10. Singer, K.; Bornstein, F. P., and Wile, S. A.: Thrombotic Thrombocytopenic Purpura: Hemorrhagic Diathesis with Generalized Platelet Thromboses, Blood **2**:542-554 (Nov.) 1947.

EFFECTS OF ACTH ON CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION

RALPH W. ALMAN, M.D.
AND
JOSEPH F. FAZEKAS, M.D.
WASHINGTON, D. C.

MENTAL aberrations, ranging from personality changes to psychoses of varying severity, have frequently been reported to follow the prolonged or intensive administration of pituitary adrenocorticotropic hormone (ACTH). Changes in mood and behavior have been described as occurring in high incidence within three days after initiation of therapy and have been correlated with electroencephalographic abnormalities appearing three to five days after ACTH treatment was begun.[1] If these alterations could be shown to be accompanied with changes in cerebral metabolism and hemodynamics, it seemed reasonable to hope that psychotic clinical states might also be presaged by detectable deviations from the normal levels of cerebral oxygen uptake and cerebral blood flow. The opportunity to investigate this premise was presented in four patients who were given ACTH in amounts too small and over too short a period to cause obvious mental changes. The hormone was administered for treatment of a variety of clinical conditions by intramuscular injection at six hour intervals. Cerebral blood flow studies were performed by the nitrous oxide method of Kety and Schmidt[2] as modified by Scheinberg and Stead.[3]

RESULTS AND COMMENT

As can be seen in the accompanying table, no appreciable changes from pretreatment levels in the mean values of cerebral blood flow, mean arterial blood pressure and cerebral vascular resistance were noted. Individual changes in these values were minor and well within the limits for normal variability and experimental error. Such changes could not be attributed to the administration of ACTH.

From the Metabolic Laboratory, Gallinger Municipal Hospital.

This investigation was supported in part by Research Grant H-556(R) from the National Heart Institute of the National Institutes of Health. The ACTH used was made available through the generosity of the Wilson Laboratories, Chicago.

1. Hoefer, P. F. A., and Glaser, G. H.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy: Electroencephalographic and Neuropsychiatric Changes in 15 Patients, J. A. M. A. **143**:620-624 (June 17) 1950.

2. Kety, S. S., and Schmidt, C. F.: The Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentrations, Am. J. Physiol. **143**:53-66 (Jan.) 1945.

3. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization, and Peripheral Resistance, with Observations on Effect of Tilting and Anxiety, J. Clin. Invest. **28**:1163-1171 (Sept., pt. 2) 1949.

The mean cerebral arteriovenous oxygen difference and, consequently, the mean cerebral metabolic rate showed a moderate decrease after ACTH therapy. The statistical significance of this observation is rendered doubtful by the small number of cases. It is entirely possible that the changes in arteriovenous oxygen difference reflect nothing more than normal day to day variations in cerebral blood flow, the semiquantitative determinations for which showed an only fortuitous agreement for each subject. This possibility is strengthened by the fact that, although apparently significant reduction in cerebral metabolic rates were noted for three subjects after ACTH, a fourth showed an increased cerebral oxygen consumption of the same magnitude. Moreover, fluctuations of this order in consecutive determinations of cerebral metabolic rate are inherent in the experimental method, as illustrated in the previous data of Kety and co-workers [4] and Scheinberg.[5] Interpretation of the effects of factors influencing cerebral metabolism must, therefore, consider statistically large numbers of determinations. The equivocal degree of change noted by

Cerebral Metabolism and Hemodynamics Before and After Administration of ACTH *

Subject	Age, Yr., Sex	Clinical Diagnosis	ACTH: Dose Until Retest, Mg.	ACTH: Days Until Retest	C. B. F. C	C. B. F. R	A.-V. O_2 C	A.-V. O_2 R	C. M. R. C	C. M. R. R	M. B. P. C	M. B. P. R	C. V. R. C	C. V. R. R
L. B.	34 F	Disseminated lupus erythematosus	360	4	57.0	62.5	4.15	2.89	2.37	1.81	105	112	1.84	1.79
D. W.	40 F	Rheumatoid arthritis	400	4	48.6	48.6	6.61	5.37	3.21	2.61	123	114	2.53	2.35
A. G.	30 F	Ménière's syndrome	260	3	52.5	53.6	5.61	6.25	2.94	3.35	92	96	1.75	1.79
J. F.	42 F	Bronchial asthma	260	3	50.8	42.8	5.89	5.16	2.99	2.21	125	130	2.46	3.04
Mean			320	3½	52.2	51.9	5.56	4.92	2.88	2.50	111	113	2.15	2.24

* C. B. F. means cerebral blood flow, expressed in cubic centimeters of blood per 100 Gm. of brain per minute; A.-V. O_2, cerebral arteriovenous oxygen difference, in volumes per cent; C. M. R., cerebral metabolic rate, in cubic centimeters of oxygen per 100 Gm. of brain per minute; M. B. P., mean arterial blood pressure, in millimeters of mercury; C. V. R., cerebral vascular resistance, in millimeters of mercury per cubic centimeter of blood per 100 Gm. of brain per minute.
C indicates values for control study before, and R retest after, administration of ACTH.

us thus needs to await further investigation. However, it appears probable that given in small doses over short periods of time ACTH does not materially affect the cerebral metabolic rate.

4. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, J. Clin. Invest. **27**:476-483 (July) 1948; The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, ibid. **27**:484-492 (July) 1948. Shenkin, H. A.; Spitz, E. B.; Grant, F. C., and Kety, S. S.: The Acute Effects on the Cerebral Circulation of the Reduction of Increased Intracranial Pressure by Means of Intravenous Glucose or Ventricular Drainage, J. Neurosurg. **5**:466-470 (Sept.) 1948. Kety, S. S.; King, B. D.; Horvath, S. M.; Jeffers, W. A., and Hafkenschiel, J. H.: The Effects of an Acute Reduction in Blood Pressure by Means of Differential Spinal Sympathetic Block on the Cerebral Circulation of Hypertensive Patients, J. Clin. Invest. **29**:402-407 (April) 1950.

5. Scheinberg and Stead.[3] Scheinberg, P.: Cerebral Blood Flow in Vascular Disease of the Brain, with Observations on the Effects of Stellate Ganglion Block, Am. J. Med. **8**:139-147 (Feb.) 1950.

SUMMARY AND CONCLUSIONS

Cerebral metabolism and hemodynamics were studied in four patients immediately before and after they had received 260 to 400 mg. of pituitary adrenocorticotropic hormone (ACTH) over three to four days. With doses of this size and administration over this period of time, no appreciable changes in cerebral blood flow or cerebral vascular resistance occurred. A small reduction in the determined value for cerebral oxygen consumption was noted; this is considered of doubtful significance.

FAMILIAL OCCURRENCE OF TUBEROUS SCLEROSIS

WILLARD W. DICKERSON, M.D.
CARO, MICH.

TUBEROUS sclerosis (epiloia) is generally considered a developmental tissue dysplasia, being an expression of anomalous development beginning in the very early months of fetal life. This disease is usually classified as belonging to the group of neurocutaneous syndromes. It is certainly congenital, and several cases have been reported which indicate that there may be a hereditary or familial component. Ross and I [1] reported that a study of the hereditary factors in this condition demonstrated these factors to be no more outstanding in patients with tuberous sclerosis than in other types of institutional epileptics.

A patient showing the characteristic symptom triad of tuberous sclerosis was admitted to the Caro State Hospital for Epileptics on April 12, 1948. She was brought to the institution by her parents and an older sister. It was immediately noticed that the female members of the family presented an unusual occurrence of this disease. The study of this family prompted the report which follows.

CLINICAL MATERIAL

FAMILY A

CASE 1.—S. A. Y. was born Aug. 3, 1938, weighing 9 pounds (4,082 Gm.). She was the last of three children. Her parents considered that she developed normally until the age of 2 years. She had begun to walk at 14 months of age and was beginning to talk; she was partially toilet trained. At 2 years of age she suffered a severe burn on her left leg. Shortly after this injury she began having "spells." At first these followed a fright or a start from a sudden loud noise. They soon occurred spontaneously and, by description, were of the grand mal type. At the age of 4 or 5 years she began to have "pimples" on her face; these have been present ever since. Although slow, she learned to talk and became nearly toilet trained. She fed herself with her fingers. As her illness progressed, she began to show no interest in her surroundings and rapidly lost all the acquirements she had once possessed. She was unable to feed herself, and all her food had to be mashed, as she could not chew. She became extremely untidy. She commenced walking on her toes and eventually became so unsteady on her feet that she would run into objects, fall and injure herself. During the last four years before admission she was kept tied in the kitchen and slept on a mat on the floor there. She usually had at least two seizures every day, but occasionally there would be a day free of attacks. She aroused the whole neighborhood by her screaming at night.

When admitted to the Caro State Hospital for Epileptics, she was 9 years old. She was obviously of idiot intelligence. She showed no comprehension of the spoken word and was resistive to every maneuver in the examination. It was necessary to confine her to her room because of her restlessness. She walked around, striking at objects and people, although there was no evidence of viciousness in her behavior; she frequently slapped herself. She showed no

Superintendent, Caro State Hospital for Epileptics.

1. Ross, A. T., and Dickerson, W. W.: Tuberous Sclerosis, Arch. Neurol. & Psychiat. **50**:233-257 (Sept.) 1943.

evidence of bowel or bladder training and drooled continually. She was unable to feed herself. There was no evidence of paralysis of any of the cranial nerves. Sebaceous adenomas were present about the nasolabial folds, cheeks and chin, arranged in typical butterfly distribution (fig. 1). The fundi were poorly visualized, but no abnormalities were seen; there was no evidence of phakomas. On examination, the heart, lungs and abdomen were found to be normal; there was no enlargement of either kidney. Both Achilles tendons were shortened. The longitudinal arches of the feet were high, and the feet flared in the anterior portions. The patient walked on her toes, with both lower extremities internally rotated. All the deep reflexes were about normal in extent. Babinski's sign was present bilaterally; there were no other pathologic toe signs. No variations from normal were demonstrable in the sensory examination. Throughout the examination, at 30 second intervals, the patient would start, the head and eyes would turn to the right and there would occur a myoclonic-like jerk of the right upper extremity.

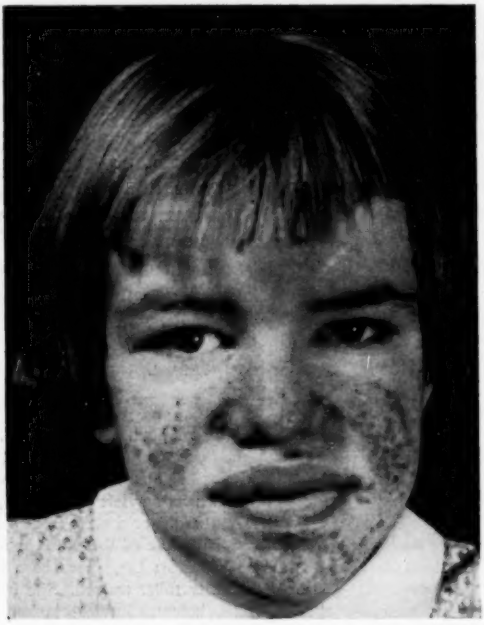


Fig. 1 (case 1).—Typical adenoma sebaceum on cheeks, nose and chin with pedunculated lesions in nasolabial folds.

Laboratory examinations revealed that the blood and urine were normal. The spinal fluid was clear and colorless and not under increased pressure. There were 6 white blood cells per cubic millimeter. Globulin was slightly increased. The colloidal gold curve was 0011000000. Roentgenograms of the head and chest were interpreted as showing a normal condition. Roentgenograms of the hands revealed no convincing evidence of abnormality. There were suggestive cystic changes in the small bones of the feet. Psychometric studies showed an intelligence quotient of 5 on the Rome adaptation of the Gesell Scale and a social maturity quotient of 5 on the Vineland Social Maturity Scale.

The first attempt at electroencephalographic recording was unsatisfactory, owing to the resistance and lack of comprehension on the part of the patient. Before the second attempt, the patient was given paraldehyde in olive oil by rectum; when this did not produce sufficient sedation, 0.2 Gm. of amobarbital (amytal®) sodium was given orally. One and one-half hours

later eight standard leads were applied, with difficulty. She was drowsy but held her eyes open in the first few minutes of the study, which was considered to reveal a sleep type of record. A summary of this examination follows:

"This record is tentatively considered to be primarily indicative of severe brain damage which involves both hemispheres, but which may be of two types. The right cortex, particularly the right motor lead, gives evidence of localized damage, which may be scar tissue, while the activity from the left hemisphere is suggestive of generalized atrophy. Sleep study (during sedation) is of diagnostic value in showing differences in interhemispheric activity in the sleep pattern. The left cortex often does not show a typical sleep pattern."

At the time of admission the patient was placed on medication consisting of phenobarbital in a dosage of ½ grain (0.032 Gm.) three times daily. In the first month of residence she had

Fig. 2 (case 2).—Typical adenoma sebaceum on nose, cheeks and chin. There are also brownish, elevated papules on the forehead and in the right brow. The herpes on the lip is coincidental.

10 grand mal seizures. The phenobarbital was then increased to ½ grain four times a day. In 1949, she had two seizures, and mesantoin® (methylphenylethylhydantoin), 1½ grains (0.097 Gm.) three times daily, was added. She has been free from seizures for 17 months.

Case 2.—M. A. Y. was 16 years old when her sister was admitted to the Caro State Hospital. She had been born by footling presentation after a normal pregnancy. She weighed 12 pounds (5,443 Gm.) at birth. When 4 months old, she had a severe attack of whooping cough, which lasted more than two months. During the course of this illness she became emaciated and presented a problem in feeding, even after her recovery. Her mother reported that shortly after this illness the child would "raise her arms, twitch her mouth and look as if she was frightened." These attacks gradually increased in severity until at 3 years of age "she had a spell that struck her to the floor." At this time a diagnosis of epilepsy was made. A few pimples appeared on her face at 4 or 5 years of age and gradually increased in number. She

did poorly in school, had numerous spells and was considered backward. When 14 years of age, she was admitted to the White Special School for Epileptics, Detroit. At that time she was having many petit mal seizures and an occasional grand mal convulsion. Many drugs, given both singly and in varying combinations, were tried, with little result. On the Detroit Learning Aptitude test she scored a mental age of 9 years 4 months and an intelligence quotient of 68.

A neurological examination in the outpatient service of the Caro State Hospital showed nothing significant other than the adenoma sebaceum (fig. 2) and the obvious mental defect. Roentgenograms of the skull revealed no evidence of cranial or intracranial calcifications. Roentgenograms of the hands and feet were not obtained. Funduscopic examination showed no phakomas or other discernible retinal changes.

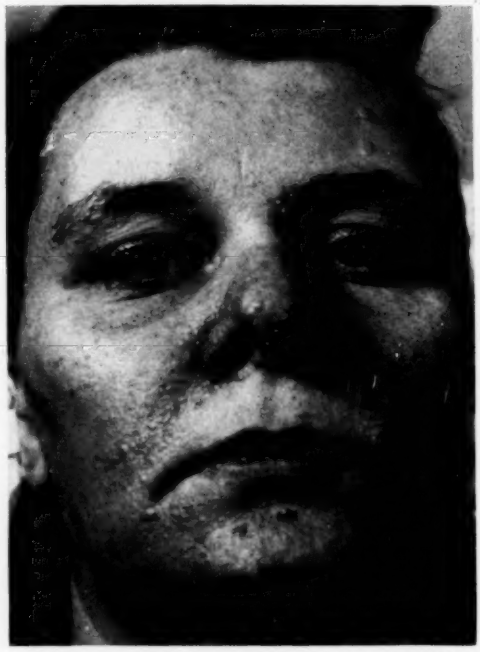


Fig. 3 (case 3).—Adenoma sebaceum in typical distribution; raised papules on forehead and chin. This woman has never had clinical evidence of epilepsy. Her electroencephalogram is normal.

An electroencephalogram gave the following impression: "The recording is considered to be borderline or mildly abnormal, with a few slow waves arising mostly from the left side. There is little resemblance to the electroencephalogram of either parent."

CASE 3.—M. Y., the mother of S. A. Y. and M. A. Y. (cases 1 and 2), was 37 when her younger daughter was admitted to the Caro State Hospital. She was of Hungarian descent and was born in Michigan. She was the first of 10 siblings; all but the youngest are living. Mrs. Y. has made inquiry and knows of no instances among her relatives of epilepsy or eruptions on the face similar to hers. She has had no serious illnesses. The eruption on her face appeared when she was 6 or 7 years old. She has never experienced any symptoms which could be considered epileptic. She completed the seventh grade in school. She married at 17, and her first child, a stillborn boy, was born on her nineteenth birthday. Her two living children, described above, represent her only other pregnancies.

Examination at the Caro State Hospital revealed only adenoma sebaceum (fig. 3). Formal testing was not done, but she gave every indication of normal intelligence. Funduscopic examination showed an entirely normal condition. Roentgenographic examination of the head showed no abnormalities or unusual calcifications.

An electroencephalogram was reported as follows: "The record is considered to be within normal limits. There is no resemblance of the recording of this patient to that of her husband or daughters."

The father has been seen and carefully interviewed; but neurological examination was not done, nor were any roentgenograms made. An electroencephalogram was reported as follows: "The record is considered to be within normal limits, although it shows a slight asymmetry of amplitude in the temporal lobe, which has no clinical significance."

At this writing, a total of 32 known patients with tuberous sclerosis have been admitted to the Caro State Hospital for Epileptics. In two other instances there has been a familial occurrence of this disease. The family of one patient was mentioned in a previous publication,[1] although at that time the occurrence of two cases of tuberous sclerosis in a single fraternity was not recognized.

FAMILY B

CASE 4.—J. C. was admitted to the Caro State Hospital on June 12, 1940, at the age of 15. He was the first child in a fraternity of five. The mother had suffered from "dizzy spells and sick headaches" throughout her pregnancy. Delivery was accomplished by a midwife after a labor lasting 12 hours. Teething began at the age of about 6 months, and there were convulsions throughout the teething period; these seizures have continued to occur. The child walked at 2½ years but has never learned to talk plainly. There were "growths" on his forehead at the age of 4. The age at which the adenomas appeared on his face is unknown.

Examination showed a white youth about 16 years old, who spoke indistinctly. There were two brownish, elevated lesions on the forehead and typical sebaceous adenomas over the face (fig. 4). There was a frequent ticlike movement of the left angle of the mouth. A typical phakoma, measuring about 1½ disk diameters in width and about 4 D. in depth, lay over the temporal margin of the left optic disk. In the right fundus, just above and nasal to the disk, was a small grayish area, thought to be a glial tumor. Routine roentgenograms of the skull showed scattered areas of increased density, varying in size from 3 to 2 cm. in diameter, throughout the cranial vault. Permission for pneumoencephalography was denied. Roentgenograms of the feet showed cystic alterations in some of the phalanges; no changes were seen in the hands. Psychometric examination showed an intelligence quotient of 19.

CASE 5.—V. C., a sister of J. C. (case 4),[2] was admitted to the Wayne County Training School, Northville, Mich., on Jan. 31, 1936. She was then 9 years old. In addition to her mental deficiency (intelligence quotient, 48), examination showed only mild hirsutism and slight facial asymmetry. On Nov. 26, 1940 ophthalmoscopic examination showed normal fundi. On March 18, 1944 she had her first known convulsion. A short time later, electroencephalograms obtained at the Neuropsychiatric Institute, Ann Arbor, Mich., were of "a borderline character, having some definite normal features in addition to quite a few atypical and abnormal features, some of them being of an epileptoid form." The whole record was "definitely abnormal and highly suggestive of an epileptic brain. There was no remarkable localizing sign of any gross lesion in the cortex." On Aug. 19, 1944 she had a second convulsion.

On Sept. 12, 1945, examination showed "a papulovascular rash over the cheeks and nose in a butterfly pattern." Atrophy of the left calf was also noted. On May 13, 1949 another convulsion occurred. She was examined in the ophthalmology outpatient department of the University Hospital, Ann Arbor, in June 1950. There, three raised, tumor-like masses were noted in the right fundus: (1) one along the superior temporal vessels, 1 disk diameter from the optic disk; (2) one along the inferior temporal vessels 3 to 4 disk diameters from the optic disk, and (3) one in the extreme nasal periphery. In the left fundus there was a large, grayish white, glistening

2. Permission to publish this case was granted by Dr. Robert H. Haskell, Superintendent of Wayne County Training School, Northville, Mich.

mound of colloid nature, projecting 3 to 4 D. into the vitreous at the inferior temporal border of the disk. "A limited x-ray examination of the skull, consisting of stereoscopic right lateral and stereoscopic posteroanterior projections, shows a mottled increase in density of various portions of the cranial vault. Furthermore, there is definite calcification in the region of the basal ganglia. The sella turcica and other structures of the base of the skull appear normal. Films of the hands and feet show minimal, but definite, wavy periosteal new bone formation on several of the metacarpals and rather pronounced periosteal thickening of the metatarsals bilaterally. The periosteal thickening is most pronounced in each second metatarsal and becomes progressively less prominent in the third, fourth and fifth metatarsals. There are a few tiny cystlike areas of bone structure in the terminal phalanges, but they are so small that their true significance is questionable." The diagnosis at the University Hospital was Bourneville's disease (tuberous sclerosis).

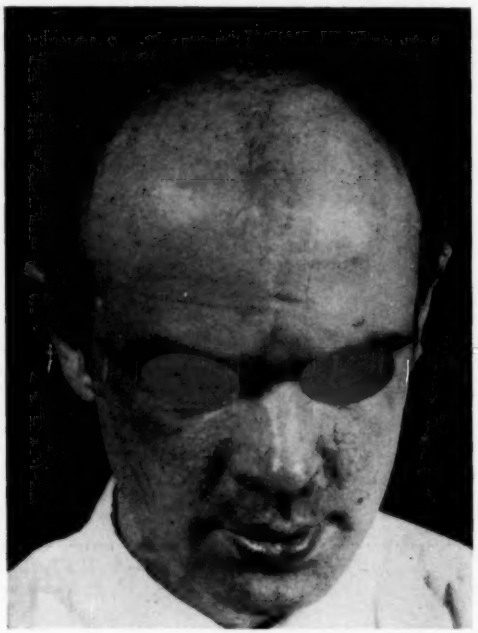


Fig. 4 (case 4).—Typical adenoma sebaceum and raised lesions on forehead.

Blood Relations.—W. C., a brother of J. C. and V. C. (cases 4 and 5), was also a patient at the Wayne County Training School. His intelligence quotient was 62. There was no clinical evidence of tuberous sclerosis or epilepsy.

B. C., a sister of J. C. and V. C., was admitted to the Caro State Hospital for Epileptics when she was 2 years old. She was a helpless, untidy idiot with a mental age of less than 3 months. Except for the extreme mental deficiency, there were no significant physical or neurological findings. She died Aug. 24, 1935, in status epilepticus, after one month of residence. Autopsy was not performed.

R. C., a twin brother of B. C., has been found to be mentally retarded. Two psychometric examinations elsewhere showed intelligence quotients of 57 and 55. He is said to have spots on his face "which have disappeared after rubbing with salve but have always returned." There is no record of physical or neurological examinations.

There are several other instances of manifestations of the various neurocutaneous syndromes on the maternal side of the family. The mother, according to her husband, had pimples on her face identical with those which my patient has. She was seen in the outpatient department of Harper Hospital, Detroit, in 1932 because of eruptions on the face and feet. Biopsy of the lesions showed them to be neurofibromas. Roentgenograms of the hands and feet showed bony changes involving the heads of the small and ring fingers of the right hand and of the great toes. At that time she gave a history of spells during childhood. Her husband said that she had had dizzy spells and headaches since the age of 17. In May 1933, after the birth of her twins, she began to have attacks of unconsciousness. She was admitted to the University Hospital, Ann Arbor, Mich., on Sept. 21, 1933, because of blindness, headaches and spells. She was confused and showed a memory defect. She was completely blind, and there was some nystagmus. Bilateral papilledema of high degree, with numerous retinal hemorrhages and bilateral paresis of the external rectus muscles, was present. "There were also multiple skin lesions over the chin, the nose, the chest and scattered elsewhere over the body—firm nodules, varying from pinhead size to the size of a bean, of whitish or yellowish color. Unfortunately, I find no detailed note in our record as to whether these skin lesions belong to the Recklinghausen group or whether they were perhaps adenoma sebaceum." Ventriculographic examination demonstrated a tumor in the suprasellar region. On Sept. 27, 1933 a large, partially intraventricular tumor from the subfrontal region, possibly arising from the septum pellucidum, was apparently completely removed. Histologically it was a glioblastoma multiforme. Postoperative infection of the wound apparently developed, and the patient died Nov. 6, 1933. Permission for autopsy was not obtained.

A brother of the mother was admitted to the Lapeer State Home and Training School as epileptic on Nov. 18, 1909. He was then 8 years old. The birth history was normal. Convulsions had begun on the third day of life and had continued at irregular intervals. He had begun to walk at 13 months of age, but his teeth did not erupt until the age of 6 years. On admission, he was unable to talk, feed or undress himself. He could take care of his toilet needs. There was a nevus on the right cheek, said to have been present from birth. He was destructive and overactive. He died in that institution on Sept. 11, 1911.

CASE 6.—F. McW., a sister of the mother, was admitted to the Caro State Hospital for Epileptics on July 17, 1941. She had had whooping cough and measles in early childhood. "Spots on the face appeared at 14 or 15 years of age." She left school at 16, when in the sixth grade. Her first seizure occurred at 24 or 25 years of age; she has had fits at irregular intervals since that time. She married at 34. Her husband was irresponsible, although apparently of normal intelligence; he was serving a prison sentence for desertion and nonsupport when his wife was admitted here. She bore three children. The oldest, a girl, was admitted to the Lapeer (Michigan) State Home and Training School on April 2, 1941, at the age of 6 years. She is still a patient in that institution. Complete examination, including electroencephalographic and pneumoencephalographic studies revealed no evidence of tuberous sclerosis. A recent psychometric examination showed a full scale intelligence quotient of 68 on the Wechsler-Bellevue Scale.

Examination of the patient at the time of admission showed the presence of adenoma sebaceum on the face (fig. 5). Nystagmus was present on deviation of the eyes in either lateral plane. Vision was 10/20 in the right eye and 20/20 in the left eye. It was the examiner's impression that optic nerve atrophy was present on the right but that the left fundus was normal. No study of the visual fields was made. Roentgenograms of the skull showed numerous discrete areas of calcification, some in the calvarium or in the cerebral cortex, some in the region of the pineal body and some in the left cerebellar hemisphere. A pneumoencephalogram showed the ventricles to be normal in size, shape and position. The calcifications seen in the plane roentgenograms appeared, in stereoscopic films, to be in the calvarium. The cortical markings were increased in width. In 1947 psychometric examination showed a mental age of 8 years 6 months and an intelligence quotient of 57 on the 1937 Stanford-Binet test, form L. Excretory pyelograms showed the right kidney to be slightly enlarged and the pelvis dilated. The left kidney and its pelvis appeared normal. The patient had a large ventral hernia through a diastasis of the rectus muscles, which had been present for many years.

Neurological examination a year after admission showed the left fundus to be normal. A tumor was present in the right eye. This tumor covered all of the optic disk except for a

narrow segment along the nasal side. It was shiny yellow and had a coarsely granular appearance, similar to that of orange peel. It was roughly oval, measuring 1½ disk diameters in width and 2 disk diameters in length. The long axis lay in the 90 degree meridian. No vessels were seen over the surface of the mass; one vessel was seen coursing along the medionasal margin to the nasal portion of the retina; another was seen emerging from beneath the mass and coursing to the upper temporal quadrant. The macula appeared normal on both sides.

Three electroencephalograms were made. The first on Aug. 19, 1946, was interpreted as a borderline slow record. The second, obtained Oct. 7, 1946, gave the impression of a "questionably normal electroencephalogram, with suspicious psychomotor paroxysmal discharges and changes in potential on the left side. Only slight changes were noted between this record and that of August 19. No valuable contribution to the impression was made with the addition of

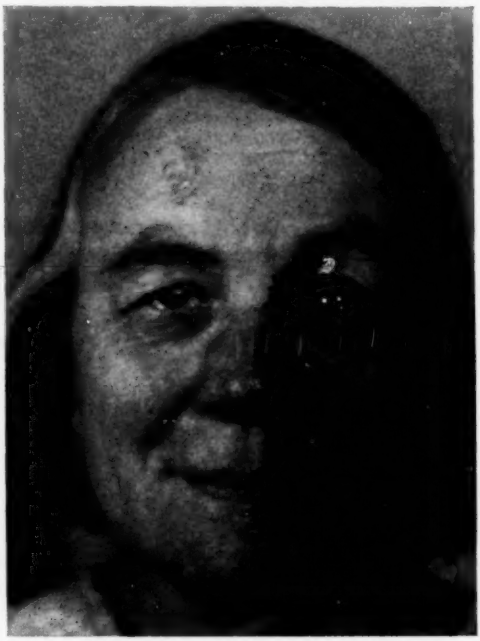


Fig. 5 (case 6).—Adenoma sebaceum on nose, cheeks and chin. There is a large raised plaque 1.5 by 1.0 cm. on the right side of the forehead.

four electrodes." The third, on Oct. 14, 1950, was summarized as follows: "The record is considered to be questionably abnormal and shows two areas of potential disturbance slightly suggestive of pathological brain changes in the right posterior quadrant with extension to the right premotor area. The basic pattern is similar to that seen on August 19 and during a semilocalization study made on October 7."

Roentgenograms of the hands and feet were reported by Dr. John Holt, University Hospital, Ann Arbor, Mich., as showing "numerous localized areas of rarefaction, some well defined and others poorly defined, involving virtually all the phalanges, as well as some of the metacarpals and metatarsals. In addition, there was some sclerosis of bone adjacent to many of the cystlike lesions which were scattered indiscriminately throughout the involved bones; furthermore, the margins of the metacarpals and metatarsals, as well as many of the phalanges, had a peculiar wavy irregularity."

The patient's course in the hospital has been uneventful. The ventral hernia was repaired surgically. At that time both kidneys were normal to palpation. On medication with phenobarbital she has averaged four seizures per year. (In the three years prior to this report she has had a total of five seizures.) She works as an ironer in the institution laundry and is considered a reliable worker. She has had two short vacations yearly with relatives.

CASE 7.[3]—M. McW., daughter of F. McW. (case 6), was admitted to the Lapeer State Home and Training School on May 7, 1941, at the age of 7 years. She was born in a hospital after a normal labor. Delivery was spontaneous and normal. Her early development was considered normal. She sat alone at 8 months but did not learn to walk alone until after her admission to the school. She had always been untidy. She had a few convulsions at the age of 3 years. It is not known when the sebaceous adenomas appeared; the record of the physical examination at admission does not mention their presence. She experienced her first

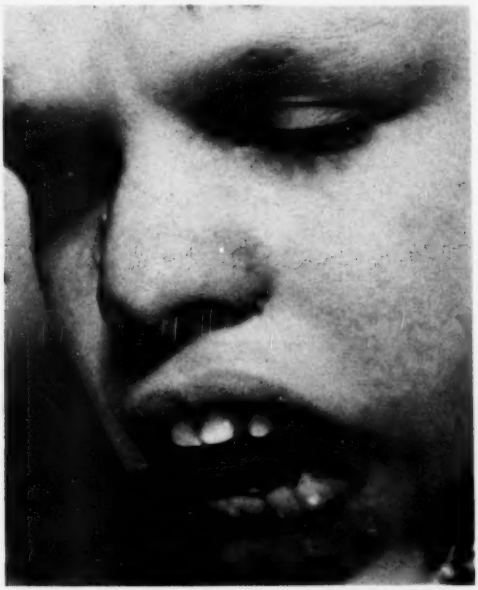


Fig. 6 (case 7).—Adenoma sebaceum on cheeks and nose. Only the larger lesions can be well seen in this photograph, which was obtained under difficulties.

seizure in the institution on April 14, 1942. Attacks have recurred at irregular intervals since that time in spite of medication.

General physical and neurological examinations showed no striking abnormalities other than the profound mental retardation and the adenomas on her face (fig. 6). Roentgenograms of the skull showed calcifications characteristic of tuberous sclerosis. Questionable early lesions were seen in roentgenograms of the hands and feet. The ocular fundi were poorly visualized, but no phakomas could be seen. In the pneumoencephalogram, the lateral ventricles appeared normal in size, but typical "candle gutterings" were present. On the Kuhlman Infant Scale, she had an intelligence quotient of 15. An electroencephalogram taken at the Caro State Hospital was reported as follows: "The sleep record is focally and paroxysmally abnormal, being equally indicative of convulsive disorders of mixed kind and damage to the right motor-

3. Permission to publish this case, and the following case, was granted by Dr. A. T. Rehn, Superintendent, Lapeer State Home and Training School, Lapeer, Mich.

temporal area of the brain. The patterns are indicative of petit mal and grand mal epilepsy. Sleep studies in the light or drifting stage are of diagnostic aid in revealing paroxysmal formations. This patient's record shows no direct similarity to any pattern shown by a blood relative, except that the patient's brother has similar focal and paroxysmal discharges during sleep recordings."

CASE 8.—M. McW., a son of F. McW. (case 6), was admitted to the Lapeer State Home and Training School on April 2, 1943. He was then 3 years old. He was delivered in a hospital, and there was no birth injury. He learned to walk but had no other accomplishments. He had had measles in infancy but no other illnesses.

Fig. 7 (case 8).—Typical adenoma sebaceum on nose, cheeks and chin; elevated plaques on forehead and right upper eyelid.

The physical and neurological status at the time of admission was within normal limits. He was able to walk with assistance. On the Vineland Social Maturity Scale he had a social maturity quotient of 30; on the Kuhlman Infant Scale his intelligence scale was 19. The age at which adenomas appeared is unknown, but they were present when an electroencephalogram was obtained at the Caro State Hospital on Nov. 20, 1950 (fig. 7). The summary of this examination follows: "This strikingly focal abnormal record is equally indicative of damage to the right cerebral hemisphere and convulsive disorders of mixed kind. There are distinct foci in the right occipital and right frontal lobes. The patterns present are indicative of petit mal, as well as grand mal, epilepsy. Sleep studies confirm the locus. There is no resemblance to the patterns of any blood relatives, chiefly because this is a sleep record. A direct comparison

would, therefore, not be valid." Roentgenograms of the skull showed a few scattered calcifications, apparently in the region of the basal ganglia. Seizures occurred at irregular intervals; the date of their onset is uncertain.

FAMILY C

CASE 9.—T. T., a white boy, was admitted to the Caro State Hospital on Dec. 21, 1946, at the age of 7 years. The parents were divorced. The father had convulsions during late childhood and in adult life; he reports that he has been free from seizures, under medication, for the last three years. It is the opinion of workers who have interviewed him that he may be feebleminded. He has been seen at the institution while visiting his children. There is no adenoma sebaceum present. An electroencephalogram, made on Oct. 30, 1950 was considered

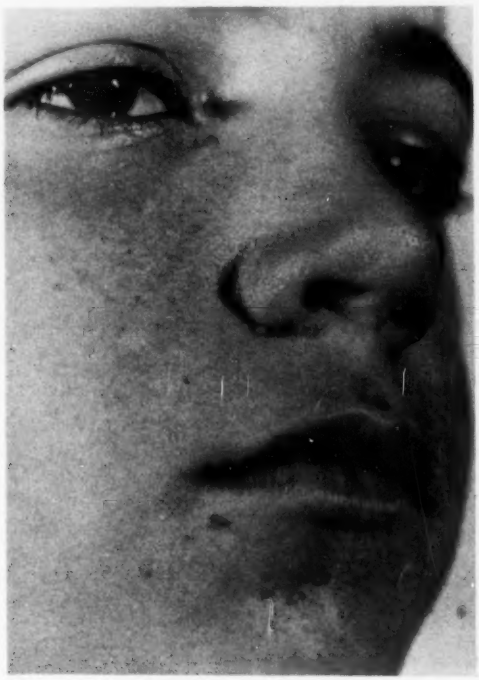


Fig. 8 (case 9).—Adenoma sebaceum, which in this case is not as prominent as in the previous case. It is present in the nasolabial folds and on the columella. There is a typical plaque below the right angle of the mouth.

to be within normal limits. His employer reports a good work record. One of his sisters has eight children, all of whom are mentally retarded. His mother is said to have been "peculiar" before her death. Several of his maternal relatives are described as high-tempered and nervous. A maternal uncle is "deformed." The electroencephalogram of the mother of the patient was normal.

The patient (T. T.) is the first of two children. His birth was reported as normal, with no injuries. He was considered slow in development. His first seizure occurred at the age of 18 months, at which time he fractured his nose. After that, attacks occurred frequently and were manifested by vomiting, unconsciousness and twitching of both arms and legs. In June 1945 a diagnosis of "idiopathic convulsive disorder, grand mal and petit mal in type" was made

at the University Hospital, Ann Arbor. As he grew older, he became increasingly irritable and was a problem because of his cruelty to animals and to his helpless sister.

Physical examination at the time of admission showed him to be of average physical development for his age. Sebaceous adenomas were present in the nasolabial folds and on the columella (fig. 8). Pigmented moles were scattered over the neck, back, shoulders and abdomen. There were three patches of vitiligo, two on the back and one on the left elbow. A café au lait spot was present in the midline over the lumbar vertebrae. There were no other unusual findings in the physical and neurological examinations. The ocular fundi were normal. Roentgenograms of the hands showed a cyst in the terminal phalanx of the right middle finger; no bony changes were seen in the feet. Roentgenograms of the skull showed disseminated small areas of calcification scattered through the basal ganglia; changes in the calvarium characteristic of tuberous sclerosis were not seen. The electroencephalogram on admission was interpreted as "paroxysmal in type, suggestive of convulsive disorders, with petit mal variant discharges. A pattern indicative of a generalized cerebral pathologic process appears in a short record." A second examination, on Oct. 30, 1950, gave the following impression: "The record is considered to be borderline abnormal, with slightly increased amplitude on the left side, suggestive of localized changes in the brain. The patient had a trial study, while an outpatient, on Sept. 19, 1946, at which time paroxysmal spike and wave formations were dominant in a short recording. It is felt that comparison of the two studies shows marked improvement." Psychometric examinations showed an intelligence quotient of 45.

Fig. 9 (case 10).—Early adenoma sebaceum. These lesions were not present when she was admitted, at the age of 4 years. They were first noticed at the age of 6½ years.

The boy is enrolled in the school program of the institution and is working at about the first grade level. He is tidy and is able to look after his own personal needs. He is unusually well behaved. He now receives 1½ grains of diphenylhydantoin sodium and ½ grain of phenobarbital three times a day. He has been free from seizures since April 1948.

CASE 10.—P. T., a sister of M. McW. (case 7), was 4 years of age when admitted to the Caro State Hospital, on Aug. 5, 1946. She was the second of the mother's two children. She was born at home, with a physician in attendance. She is able to sit up but otherwise does not help herself in any way. She has always been a difficult child to feed; she swallows air, and the resulting distention of the abdomen is frequently troublesome. Seizures began at the age of 1 month and, as described, are of both grand and petit mal types; at the time of her admission they were occurring at the rate of three or four a week.

The physical and neurological status was essentially within normal limits. The face was slightly asymmetrical, and the right palpebral fissure was a bit narrower than the left. No adenoma sebaceum was noticed. There was external strabismus of the right eye. The fundi were poorly seen; no phakomas were apparent. The deep reflexes were questionably hypoactive, and there were no pathological toe signs.

Routine laboratory studies, including examination of the spinal fluid, showed no abnormalities. It was possible to obtain an electroencephalogram only after sedation with secobarbital (seconal®) sodium. The summary of this examination follows: "This grossly abnormal record shows evidence of petit mal and grand mal epilepsy in a pattern that is equally indicative of severe and widespread degenerative changes. There appears to be lateralization to the right hemisphere. It is questionable whether the patient was sleeping in any part of the study, although she was receiving a sedative. In view of the multiple phase differences, it is felt that there are separate areas of great pathological change in both hemispheres, but more pronounced on the right than on the left side. A previous attempt at recording on Oct. 4, 1946 was a failure."

Recently it was noted that sebaceous adenomas were present on the face (fig. 9). Roentgenograms of the skull showed an area of calcification in the left temporo-occipital region. Throughout this area could be seen lines of double contour similar to those seen in cases of the Sturge-Weber syndrome. There were no hemangiomas on the face or elsewhere on the body. Roentgenograms of the hands and feet showed no changes from normal.

REVIEW OF THE LITERATURE

In the extensive literature on the syndrome known as tuberous sclerosis there are relatively few instances of its appearance in more than one member of a family. In most of the reported cases no mention is made of relatives similarly afflicted, and there is no indication of how frequently this circumstance actually occurs. For convenience, the recorded instances of familial occurrence are divided into cases appearing in the same and in different generations.

A. Occurrence in Three Generations.—Kirpicznik [4] and Berg [5] reported the appearance of tuberous sclerosis in members of three generations of one family. The grandfather died of a hypernephroma. The father had adenoma sebaceum, renal tumor and epilepsy. The patient, a female idiot of 8 years, likewise had adenoma sebaceum, renal tumor and epilepsy. Her brother, with intraventricular and renal tumors, had died at the age of 28.

Quill and Marting [6] found eight cases of the disease in three generations of one family. The grandmother had seizures, adenoma sebaceum and tumors of the nail

4. Kirpicznik, J.: Ein Fall von tuberöser Sklerose und gleichzeitigen multiplen Nierengeschwülsten, Arch. path. Anat. **202**:358-376 (Dec.) 1910.

5. Berg, H.: Vererbung der tuberösen Sklerose durch zwei bzw. drei Generationen, Ztschr. ges. Neurol. u. Psychiat. **19**:528-539 (Sept.) 1913.

6. Quill, L. M., and Marting, E. C.: Epiloia: Report of Cases, Surgery **9**:581-590 (April) 1941.

beds. One daughter also had adenoma sebaceum and subungual fibromas but no epilepsy. This daughter had four children—two boys and two girls. The boys had epilepsy, adenoma sebaceum and subungual tumors. One of the girls had sebaceous adenomas but no epilepsy and was of average intelligence; the other was a helpless idiot with adenoma sebaceum, epilepsy and tumors of the nail beds. A sister of the mother of the four children had petit mal attacks, adenoma sebaceum and subungual fibromas. Her son died of a brain tumor, which at autopsy was shown to be tuberous sclerosis.

Koenen [7] cited the instance of an alcoholic who had adenoma sebaceum, a patch of shagreen skin in the lumbar region and subungual fibromas. He did not have epilepsy, but a nephew had seizures. This man had two daughters and a son. One daughter had epilepsy, adenoma, pedunculated fibromas and shagreen skin. The other daughter had no cutaneous lesions, but had petit mal attacks, beginning at 4 years, and grand mal attacks, at 18. She had two daughters—one with fibromas and shagreen skin; the other with convulsions in infancy, "absences" in childhood and shagreen skin.

Critchley and Earl [8] described a family in which the grandfather, father and a daughter were all afflicted.

B. Occurrence in Two Generations.—Urbach and Weidmann [9] published a report of a man with adenoma sebaceum who had 11 children. One girl, feebleminded and with a cardiac defect, had no cutaneous changes. Five children were normal. One boy had adenoma sebaceum with other cutaneous changes and a cardiac lesion. One girl had adenoma sebaceum only; one had adenoma sebaceum, epilepsy and imbecility; one had adenoma sebaceum and imbecility but no epilepsy.

Messinger and Clarke [10] reported the case of a man with tuberous sclerosis, including retinal tumor, whose father also had tuberous sclerosis.

Duwé and van Bogaert's [11] patient had had tumors on his face (adenoma sebaceum) since his first communion. He was mentally retarded but had never had epilepsy. He also had a huge tumor in the lumbar region, which had appeared at the age of 17, and several pedunculated moles on the neck. His brother had six children, one of whom was epileptic and hydrocephalic and died at 11 years of age, of hydrocephalus and cerebral tumor. Another died of cystic kidney. An epileptic sister had two epileptic children, one of whom was severely retarded mentally.

Ley [12] described a case with clinical evidence of tuberous sclerosis. Of the patient's seven sisters, one had a facial hemangioma, and one, with a convulsive

7. Koenen, J.: Een familiare, hereditaire vorm van tubereuse sclerose, Nederl. tijdschr. geneesk. **75**:731-738 (Feb. 14) 1931.

8. Critchley, MacD., and Earl, C. J. C.: Tuberose Sclerosis and Allied Conditions, Brain **55**:311-346 (Sept.) 1932.

9. Urbach, E., and Wiedmann, A.: Morbus Pringle und Morbus Recklinghausen: Ihre Beziehungen zueinander, Arch. Dermat. u. Syph. **158**:334-343, 1929.

10. Messinger, H. C., and Clarke, B. E.: Retinal Tumors in Tuberous Sclerosis: Review of the Literature and Report of a Case, with Special Attention to Microscopic Structure, Arch. Ophth. **18**:1-11 (July) 1937.

11. Duwé, G., and van Bogaert, L.: Adénomes sébacés du type Pringle avec fibromatose cutanée dans une famille atteinte de sclérose tubéreuse, J. belge neurol. et psychiat. **33**:749-751 (Nov.) 1933.

12. Ley, A.: Sclérose tubéreuse de Bourneville sans troubles mentaux avec hérédité similaire dans la descendance, J. belge neurol. et psychiat. **33**:684-687 (Oct.) 1933.

son, had disseminated tumors of the skin. One of his five brothers died in convulsions as an infant, and a nephew was an idiot. The patient had three children. The oldest, a girl, was a profound idiot who died in convulsions at the age of 4 years. The two youngest were severely defective and epileptic. Both had adenoma sebaceum and disseminated cutaneous fibromas.

Borremans, Dyckmans and van Bogaert [13] reported a family with several cases of tuberous sclerosis. In their first patient, a woman, petit mal had developed at 7, adenoma sebaceum at 8 and grand mal at 26 years of age. She also had shagreen skin in the lumbar region, subungual fibromas and a retinal phakoma. Two children of one of her sisters had died in convulsions. The patient had 11 children, the second of whom died in convulsions. The third, a boy (case 2), was retarded and could barely read and write. Seizures began at the age of 4, and adenomas appeared on the face at the age of 8. There was a patch of shagreen skin in the lumbar region. There were no subungual tumors or phakomas. The fourth child (case 3), also a boy, was of diminished intelligence but had neither adenomas nor shagreen skin; he did have a few warts. The sixth child, a boy, died at the age of 6 years. He was an idiot in whom, at 1½ years of age, there developed convulsions and, at 5 years, adenoma sebaceum. At the age of 5½ years flaccid paraplegia appeared. In the eighth child (case 4) epilepsy developed at 4 and adenomas at 7 years of age. The ninth child (case 5) had epilepsy at 4 and adenomas at 10 years of age. The tenth child had adenomas at 1 year and convulsions at 14 months of age and died in a convulsion at the age of 18 months. The last child died in a convulsion at the age of 6 months.

Apley's [14] cases were those of father and son. The father had epilepsy, adenoma sebaceum, cerebral calcifications, phakomas and mild mental deficiency. The son was epileptic and mentally retarded. He had sebaceous adenomas and cerebral calcifications but no phakomas.

Schuster [15] described the case of a boy, aged 16, with congenital heart disease, adenoma sebaceum, epilepsy and signs of intracranial tumor. Autopsy showed tuberous sclerosis. His mother had multiple café au lait spots and a nevus on the left arm. Her sister was epileptic. The maternal grandmother was epileptic and had numerous pigmentations of the skin.

Lichstein and Solis-Cohen [16] published the report of a father and son supposedly with this syndrome. The father had had two fits 12 years apart. The physical and neurological status was normal, as were the eyegrounds. Roentgenograms of the skull showed one or two small calcium deposits in the region of the left ventricle. The son, aged 22, had been a confirmed epileptic since the age of 2 years and was having from eight to 10 fits a day. He had no facial lesions, but there was decided mental retardation. Large, macular, atrophic lesions were present in the ocular

13. Borremans; Dyckmans, and van Bogaert, Y.: Études cliniques, généalogiques et histopathologiques sur les formes hérédofamiliales de la sclérose tubéreuse, J. belge neurol. et psychiat. **33**:713-746 (Oct.) 1933.

14. Apley, J.: Familial Tuberose Sclerosis with Calcification: Report of 2 Cases, Brain **67**:258-264 (Sept.) 1944.

15. Schuster, P.: Beiträge zur Klinik der tuberösen Sklerose des Gehirns, Deutsche Ztschr. Nervenh. **50**:96-133 (Sept.-Oct.) 1914.

16. Lichstein, J., and Solis-Cohen, L.: Familial Tuberous Sclerosis (Epiloia) Without Adenoma Sebaceum: Report of 2 Cases, J. A. M. A. **122**:429-432 (June 12) 1943.

fundi. Roentgenograms of the skull showed calcified deposits throughout. Pneumoencephalograms revealed calcium deposits in the ventricles. Merritt and Aring [17] and Koch [18] suggested that the proper diagnosis in these cases was toxoplasmosis.

Glicklich, Schultz and Benjamin's [19] patient was a soldier who had had a total of five seizures. Typical adenomas were present, and he was of borderline intelligence. Irregularities in the walls of the lateral ventricle were seen in the pneumoencephalogram. A phakoma was present on the right optic disk. His father was hopelessly limited, both mentally and physically, and had a cutaneous condition, involving the face and nose, similar to the patient's. One of his two sisters had adenomas on the face. Of four brothers, only one was living. This brother had cutaneous lesions similar to the patient's and appeared mentally retarded. He had had epilepsy for four years as a child. The youngest of the deceased brothers was always an invalid of low mentality and had had seizures from the age of 4 years until his death, at 20.

C. Occurrence in the Same Generation.—Miles and Dixon [20] and also Friedman [21] reported the cases of three siblings, one girl and two boys, aged 10 years, 8 years and 22 months, respectively. All had epilepsy and cerebral opacities in roentgenograms of the skull. The girl had sebaceous adenomas and lesions in the ocular fundi. The oldest boy had adenomas, lesions in the fundi and a shagreen patch over the left eye. The father had abnormal fundi, but no phakomas, and many moles, but no adenomas.

Jones and Prior [22] described three affected members in one family. The oldest, a girl aged 5 years, had adenoma sebaceum, a patch of shagreen skin over the sacrum and epilepsy. She was of normal intelligence. The next girl, aged 2½ years, was an epileptic imbecile with leukoderma but no adenomas. The youngest, a boy aged 5½ months, was epileptic. The authors mentioned that the father had an adenomatous rash about both sides of the mouth, but epilepsy was not mentioned. A sister of the father had leukoderma.

Van Bouwdijk Bastiaanse and Landsteiner [23] recorded the highest incidence of the disease in a single generation of one family. The oldest child, a boy, had tuberous sclerosis, confirmed by autopsy. The second son was epileptic. The next, a girl, had several nevi and a tumor in the left retina. Van der Hoeve found retinal tumors in one of her five children. The fourth child, a girl, had no adenomas but did have a patch of shagreen skin; van der Hoeve again found retinal tumors. Autopsy confirmed the diagnosis of tuberous sclerosis. The next daughter, without epilepsy

17. Merritt, H. H., and Aring, C. D.: Familial Tuberous Sclerosis, J. A. M. A. **122**:892 (July 24) 1943.

18. Koch, F. L. P.: Tuberous Sclerosis and Toxoplasmic Encephalomyelitis, J. A. M. A. **122**:1267 (Aug. 28) 1943.

19. Glicklich, E. A.; Schultz, A., and Benjamin, J. E.: Tuberous Sclerosis Associated with Tumor of the Optic Disk (Phakoma), Arch. Ophth. **32**:60-62 (July) 1944.

20. Miles, P. W., and Dixon, J. M.: Tuberous Sclerosis in 3 Siblings, Arch. Ophth. **41**: 473-480 (April) 1949.

21. Friedman, R.: Tuberous Sclerosis, presented at the Clinical Conference at St. Louis Children's Hospital, J. Pediat. **32**:589-594 (May) 1948.

22. Jones, S. E., and Prior, G. P. U.: Tuberose Sclerosis or Epiloia: Three Cases in One Family, M. J. Australia **1**:857-858 (May 14) 1938.

23. van Bouwdijk Bastiaanse, F. S., and Landsteiner, K.: Een familiare vorm van tubereuse sclerose, Nederl. tijdschr. geneesk. **66**:718-719 (Feb. 18) 1922.

or cutaneous lesions, died with symptoms of cerebral tumor. Autopsy showed tuberous sclerosis. The sixth, a girl, was normal. The seventh, a son, had petit mal, adenomas and a phakoma. The next son was normal. The last son experienced absences. He died at the age of 4 years, and autopsy demonstrated the presence of tuberous sclerosis. This is probably the same family as that reported by van der Hoeve.[24]

Patient 3 in Butterworth and Wilson's [25] series was a man of 22. He had two brothers who were below normal mentally and who displayed epileptic equivalents and had "blood freckles," possibly sebaceous adenomas. The mother of their sixth patient was of subnormal intelligence and died of a brain tumor.

Fabing [26] described twin sisters, each of whose cutaneous lesions (and hemiparesis) were mirror images of the other's.

Hopwood [27] found the condition in one of dissimilar male twins.

Paillas and Cain [28] suggested the diagnosis of tuberous sclerosis for the disorder in girl twins. One had adenoma sebaceum, recurrent convulsions, beginning at the age of 6 years, and mental retardation. Hemiparesis developed after a seizure. The other had convulsions, beginning at the age of 5, and was also mentally retarded. Both had diffuse intracranial calcifications.

Brushfield and Wyatt [29] mentioned, among their 16 cases, that of a girl with tuberous sclerosis whose mother had died in an asylum. The patient had a brother with adenoma sebaceum who was of normal intelligence.

Gunther and Penrose [30] studied the families of 20 patients with tuberous sclerosis. In three families, one parent was considered to have an incomplete form of epiloia. In three families, one sibling had fully developed epiloia. In 10 siblings, represented by eight families, incomplete forms were found.

In Ferraro and Doolittle's [31] series their first and second patients were sisters. The mother of their third patient died of a hypernephroma.

COMMENT

Actually, in few cases of tuberous sclerosis are the signs and symptoms limited to the classic triad of idiocy, epilepsy and adenoma sebaceum. One may mention many other concomitant features, one or more of which occur in practically every case—café au lait spots; nevi; subungual fibromas; shagreen skin; leukoderma or

24. van der Hoeve, J.: Augengeschwülste bei der tuberösen Hirnsklerose (Bourneville) und verwandten Krankheiten, Arch. f. Ophth. **111**:1-16 (March) 1923.

25. Butterworth, T., and Wilson, M., Jr.: The Dermatologic Aspects of Tuberous Sclerosis, Arch. Dermat. & Syph. **43**:1-41 (Jan.) 1941.

26. Fabing, H.: Tuberous Sclerosis with Epilepsy (Epiloia) in Identical Twins, Brain **57**:227-238 (Oct.) 1934.

27. Hopwood, A. T.: Tuberous Sclerosis: Report of Five Cases Including One Case in One of Twins, Ohio State M. J. **33**:277-282 (March) 1937.

28. Paillas, J. E., and Cain, J.: L'épilepsie chez les jumeaux, France méd. **10**:8-9 (June) 1947.

29. Brushfield, T., and Wyatt, W.: Epiloia, Brit. J. Child. Dis. **23**:178-185 (July-Sept.) 1923.

30. Gunther, M., and Penrose, L. S.: The Genetics of Epiloia, J. Genetics **31**:413-430 (Oct.) 1935.

31. Ferraro, A., and Doolittle, G. J.: Tuberous Sclerosis: Studies in Psychiatry, New York Psychiatric Society, 1937, vol. 8, pp. 1-52.

vitiligo; retinal tumors or phakomas; tumors of the kidney, thyroid, heart muscle or lung; intraventricular tumors; areas of increased radiopacity in the calvarium and other flat bones, and cystic changes in bone, especially in the phalanges. Periosteal changes are commoner in the metatarsals.

Moolten [32] pointed out that the lesions in other organs were of the nature of hamartomas and that the primary abnormality lay in the faulty differentiation of tissues, rather than body units. He believed that, because other organs were involved simultaneously with the brain, the term tuberous sclerosis, which refers only to the cerebral lesions, should be reserved for them and should not be used to designate the syndrome as a whole.

Critchley and Earl described four abortive and latent forms of tuberous sclerosis: (1) adenoma sebaceum alone, (2) adenoma sebaceum with epilepsy and without mental defect, (3) adenoma sebaceum with symptoms pointing to intracranial neoplasm and (4) visceral tumor alone with a familial history of tuberous sclerosis. Butterworth and Wilson classified the clinical variations of tuberous sclerosis, or formes frustes, as follows: (1) adenoma sebaceum alone, (2) epilepsy alone, (3) mental deficiency alone, (4) adenoma sebaceum with mental deficiency, (5) adenoma sebaceum with epilepsy, (6) epilepsy with mental deficiency, (7) adenoma sebaceum with symptoms of cerebral tumors and (8) visceral tumors alone (including retinal tumors).

Standard textbooks on dermatology describe adenoma sebaceum as usually occurring in mentally retarded persons and mention its occasional occurrence in tuberous sclerosis. There is no doubt that adenoma sebaceum occurs in persons of normal mentality and that it also sometimes shows a familial tendency. Shelmire [33] reported five cases in a single family—those of the father, three daughters and a son, "all of whom were country folk of more than average appearance and intelligence. No epilepsy was observed." He mentions a report by Taylor of three cases in one family. In the discussion of Shelmire's paper, Mitchell stated that he had seen three cases in one family—those of a mother and two daughters. The children were abnormally bright. Reitmann [34] described the appearance of adenoma sebaceum without tuberous sclerosis in four generations. Riehl [35] described the occurrence of adenoma sebaceum alone in identical twins. Fuhs [36] traced the condition through five generations. Woolhandler and Becker's [37] fourth patient, a woman, had a father and brother with similar lesions, but her mother and sister were not affected.

32. Moolten, S. E.: Hamartial Nature of the Tuberous Sclerosis Complex and Its Bearing on the Tumor Problem: Report of a Case with Tumor Anomaly of the Kidney and Adenoma Sebaceum, Arch. Int. Med. **69**:589-623 (April) 1942.

33. Shelmire, J. B.: Adenoma Sebaceum: A Report of Five Cases in One Family, J. A. M. A. **71**:963-965 (Sept. 21) 1918.

34. Reitmann, K.: Zur Kenntnis des Adenoma sebaceum Pringle (Naevus multiplex Pringle), Arch. Dermat. u. Syph. **83**:177-186, 1907.

35. Riehl, G.: Adenoma sebaceum Pringle (Demonstration), Wien. klin. Wchnschr. **19**: 1298-1299 (Oct.) 1906.

36. Fuhs, H.: Über Naevus multiplex Pringle, Arch. Dermat. u. Syph. **148**:509-515 (April) 1924-1925.

37. Woolhandler, H. W., and Becker, S. W.: Adenoma of Sebaceous Glands (Adenoma Sebaceum), with Consideration of Keratotic Adenoma Sebaceum and True Adenoma of Sebaceous Glands, Arch. Dermat. & Syph. **45**:734-756 (April) 1942.

Klauder [38] cited the case of a 13 year old girl with adenoma sebaceum alone whose father, uncle, grandfather and great uncle all had the same lesions.

Critchley and Earl suggested it was not unlikely that slight alterations occur in the cerebral cortex of such persons, differing only in degree from those in tuberous sclerosis. Cockayne [39] asserted that "it is well established that adenoma sebaceum may occur without brain tumors and tuberous sclerosis without adenoma sebaceum." However, autopsy evidence is lacking to indicate whether or not in such cases of adenoma alone there is definite involvement of the cerebral cortex or other divisions of the central nervous system.

At the Caro State Hospital, tuberous sclerosis has been found at autopsy in only one case in which there was no adenoma sebaceum. This was the case of a severely retarded girl, aged 6 years at the time of death. In our previous study,[1] it was found that the usual age of appearance of the adenomas was about 5 years. In the present series they appeared at the ages of 4, 4, 6, 4, 18, 14, 8 and 10 years, respectively. It is believed that had this patient lived, the characteristic lesions on the face would probably have developed. This possibility has also been suggested by Ferraro and Doolittle. As far as I have been able to find, there are no conclusive reports to support Cockayne's statement that tuberous sclerosis may occur without adenoma sebaceum, if the age of the patient is taken into account.

Several authors have expressed the opinion that tuberous sclerosis is hereditary, although none have been able to delineate clearly the mode of transmission. Cockayne expressed the opinion that the disease is an incompletely dominant trait. He was unable to state what it would be like in the homozygous state but was certain that in the heterozygous state it showed great variation. That heterozygotes are sometimes indistinguishable from normal persons accounts for a number of isolated cases. Gunther and Penrose concluded that if the condition is dominant the gene is incomplete, explaining the frequency of incomplete forms. It was their opinion that a single, rare, dominant gene is the causative factor. Quill and Marting agreed with Gunther and Penrose that the disease is not a recessive, but, rather, is a dominant characteristic which tends to be incomplete. The presence of nail bed tumors in all their cases led to the presumption that epiloia is transmitted even in its minute details.

It is evident that others of the less constant features associated with tuberous sclerosis also have a decided tendency toward familial appearance. Nail bed tumors appeared in all of Quill and Marting's cases. Cerebral calcifications were present in the families of Apley and Miles and Dixon. Retinal tumors were prominent in the family of van Bouwdijk Bastiaanse and Landsteiner, as they are in cases 4, 5 and 6 of the present series. The cystic changes seen in the phalanges and the periosteal changes in the metatarsals occur in cases 6, 7 and 8 of this series. Renal tumors were prominent in the families of Kirpicznik and Berg and Messinger and Clarke. Patches of shagreen skin were encountered in the families mentioned by Koenen and Borremans, Dyckmanns and van Bogaert. There is some evidence in family B in the present study that the osseous changes in the hands and feet may be a familial trait.

38. Klauder, J.: Adenoma Sebaceum, Arch. Dermat. & Syph. **7**:849 (June) 1923.

39. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933, pp. 289-293.

Another factor to be considered is the close relation of tuberous sclerosis to other neurocutaneous syndromes, particularly Recklinghausen's disease. Yakovlev and Guthrie [40] mentioned the overlapping of signs and symptoms in tuberous sclerosis, neurofibromatosis and encephalotrigeminal angiomatosis. I have mentioned the frequent occurrence in patients with tuberous sclerosis of lesions of the skin other than adenoma sebaceum. Café au lait spots are as frequent in neurofibromatosis, if not more so. Tumors of the retina occur in both syndromes. The mother of patients 4 and 5 presented an interesting combination of the two syndromes, and her brother had a nevus on the face. A sister of Ley's patient likewise had a facial hemangioma. In case 10, the clinical picture is that of tuberous sclerosis, but the roentgenographic findings are those of encephalotrigeminal angiomatosis.

In attempting to trace the hereditary factors in tuberous sclerosis, is one studying a single disease entity? Cases of tuberous sclerosis with signs and symptoms limited to the classic symptom triad certainly are infrequent. One wonders whether it might be more profitable to study the group of neurocutaneous syndromes as a whole than to attempt to confine the effort to a single, poorly limited entity within the larger group.

SUMMARY

An attempt to trace the hereditary factors in three family groups of tuberous sclerosis reveals no clearcut pattern of transmission. In each family, the picture is complicated either by formes frustes or by various combinations of other neurocutaneous syndromes. It is suggested that it might be more profitable to consider such factors for the entire group of neurocutaneous syndromes, rather than for a single entity within the group.

40. Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145-1194 (Dec.) 1931.

NEUROLOGICAL COMPLICATIONS OF INSULIN SHOCK THERAPY WITH ELECTROENCEPHALOGRAPHIC STUDIES

Case Studies

LOUIS HALLE, M.D.
AND
J. F. ROSS, M.D.
CLEVELAND

THERE are numerous reports of neurological and psychiatric changes occurring as result of hypoglycemia. Many of these are described as complications of insulin overdosage in diabetic patients [1] or of hyperinsulinism in patients with pancreatic adenoma.[2]

In the literature on insulin coma treatment of schizophrenia there are also many such reports. These have been collected and summarized by Spencer.[3] In his thorough collation he includes reports of confused, stuporous states; motor and sensory aphasias; various paralyses, such as monoplegias, facial pareses and hemiplegias, and dysarthrias and rotary movements. There is no general agreement on the incidence of such complications. Fleeting sensory disturbances, such as numbness and tingling of extremities and impairment of taste, have also been reported as occurring as a possible transient change in the central nervous system of patients receiving insulin or as result of vitamin B deficiency. These complications may occur as sequelae to a prolonged coma or may appear immediately after termination

From the Veterans Administration Hospital, Cleveland.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and the conclusions published by the authors are the result of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Murphy, F. D., and Purtell, J.: Insulin Reaction and Cerebral Damage That May Occur in Diabetes, Am. J. Digest. Dis. **10**:103 (March) 1943. Klein, F., and Ligterink, J. A.: Insulin and Cerebral Damage, Arch. Int. Med. **65**:1085 (June) 1940. Sherrill, J. W., and MacKay, E. M.: Deleterious Effects of Experimental Protamine Insulin Shock, ibid. **64**:907 (Nov.) 1939. Winkler, J. L.: Fatal Hypoglycemia in Diabetes, Lancet **1**:215 (Feb.) 1948. Jones, G. M.: Posthypoglycemic Encephalopathy: Case Reports, Am. J. M. Sc. **213**:206 (Feb.) 1947.

2. (*a*) Kerwin, A. J.: Fatal Hyperinsulinism with Cerebral Lesions Due to Pancreatic Adenoma, Am. J. M. Sc. **203**:363 (March) 1942. (*b*) Hoefer, P. F. A.; Guttman, S. A., and Sands, I. J.: Convulsive States and Coma in Cases of Islet Cell Adenoma of the Pancreas, Am. J. Psychiat. **102**:486 (Jan.) 1946.

3. Spencer, A. M.: Post-Hypoglycaemic Encephalopathy in Sakel's Insulin Treatment, J. Ment. Sc. **94**:513 (July) 1948.

of the usual coma period. They last from a few hours to a few days.[4] Organic dementia [5] and the Korsakoff syndrome [6] lasting weeks to months have also been reported.

In case reports of complications of profound hypoglycemia there are relatively few references to electroencephalographic studies. Allan and Crommelin [7] had a six year old diabetic girl who received a dose of 25 U. S. P. insulin units of protamine zinc insulin and lapsed into coma. When roused finally, she had right hemiplegia, aphasia and right-sided convulsive seizures. The electroencephalogram showed diffuse abnormal activity, that from the left hemisphere being more pronounced, without, however, being limited to any particular part. Proctor and Easton [8] reported the case of a woman, aged 26, with "schizo-affective psychosis" who received 220 units of insulin on the twenty-ninth treatment day to initiate the seventh coma period. She had a prolonged coma, lasting approximately four days. An electroencephalogram on the second day of coma showed 5 to 6 cycle per second waves with some delta activity. The pretreatment electroencephalogram and a tracing taken three months after treatment were normal. Goldfarb and Laughlin [9] also described a case of prolonged coma as a complication of shock treatment in a man, aged 30, and gave an electroencephalographic report. However, it is not stated when the record was made except that it was after a period of coma that lasted 96 hours. The patient had received 115 units of insulin to initiate the fourth coma period. Neurologically, the patient presented at first many rigidities, "alternating with flaccid relaxation of the entire body, fixed pupils and dissociated ocular movements." For a few hours on the second day of coma "he presented a left-sided facial weakness which disappeared, transient irregularities of his deep reflexes, slight nuchal rigidity, and possible Kernig responses." These had all disappeared by the fourth day. The electroencephalogram showed "an unusually wide spread of alpha frequencies. Analysis showed the dominant components to be at 7, 10, 12 and 14 cycles per second." The authors stated that "this record is barely outside the normal range and suggests a very slight degree of residual cortical change."

Unlike other organs which can utilize carbohydrate, protein and fats for energy requirements, the brain is able to oxidize carbohydrate only.[10] It is also well known

4. Stern, K.; Dancey, T. E., and McNaughton, F. L.: Sensory Disturbances Following Insulin Treatment of Psychoses, J. Nerv. & Ment. Dis. **95**:183 (Feb.) 1942.

5. Wechsler, Z.: Unusual Complication in Protracted Insulin Shock Treatment, M. J. Australia **2**:616 (Dec.) 1944.

6. Milch, E. C., and Bolles, M. M.: A Case of Prolonged Coma Following Insulin with Eventual Recovery, J. Nerv. & Ment. Dis. **88**:817 (Dec.) 1938.

7. Allan, F. N., and Crommelin, R. M.: Cerebral Damage from Insulin "Shock": Hemiplegia, Aphasia and Epileptic Seizures for 15 months, J. A. M. A. **118**:373 (Jan.) 1942.

8. Proctor, L. D., and Easton, N. L.: Unusual Case of Prolonged Coma in Hypoglycemic Shock Treatment, Am. J. Psychiat. **99**:203 (Sept.) 1942.

9. Goldfarb, W.; Laughlin, J. M., and Kiene, H. E.: Prolonged Insulin Shock, Am. J. Psychiat. **101**:827 (May) 1945.

10. Lennox, W. G.: The Cerebral Circulation: XIV. Respiratory Quotient of the Brain and of the Extremities in Man, Arch. Neurol. & Psychiat. **26**:719 (Oct.) 1931. Himwich, H. E., and Nahum, L. H.: Respiratory Quotient of the Brain, Am. J. Physiol. **101**:446 (Aug.) 1932.

that the brain is most susceptible of all organs to lack of oxygen. The reciprocal relationship between oxygen and carbohydrate in brain metabolism is well established. Reduction in the sugar content of the blood reduces the oxidative processes of the cells to such a degree that the effects are similar to those of anoxia.[11]

In insulin coma treatment, the progressive neurological signs and symptoms which develop have been fully described in five stages.[12] These stages correspond to the anatomical levels of forebrain (cerebral cortex), diencephalon, midbrain, upper medulla and lower medulla. The level more recent in phylogenetic development and more complex in function suffers first from hypoglycemia because of the greater metabolic requirement. Hoefer and associates,[2b] in their article on neurological complications seen in hyperinsulinism, stated that the selection of the site of complication is likewise due to these differences in metabolic needs.

The electroencephalographic signs of reduced oxygen and/or reduced carbohydrate closely parallel the clinical findings. Davis [13] showed that the lowering of blood sugar in normal young adults by injection of insulin (0.05 unit of insulin per kilogram of body weight) caused replacement of normal alpha activity in the electroencephalogram by slower waves, chiefly of 6 to 8 per second frequency. The electroencephalogram returned to normal with the restoration of the blood sugar level, but the electroencephalographic changes lagged 10 minutes or more behind the blood sugar changes. Finesinger and associates [14] studied the effect of reduced oxygen tension on the electroencephalogram of psychoneurotic patients and controls. The electroencephalograms showed a shift to slow frequencies during low oxygen tension. It is apparent that there is great individual variation in the blood sugar level at which slow activity appears. In a study by Brazier and associates,[15] 13 per cent of their series of electroencephalograms of 45 normal adults showed no alteration with hyperventilation, even during reduction of the blood sugar to 40 mg. per 100 cc. with insulin.

Alterations in the electroencephalogram during insulin shock treatment also paralleled the level of the blood sugar. Himwich and associates,[12] Hoagland, Rubin and Cameron,[16] and Hoagland, Cameron and Rubin [17] showed a progressive decline

11. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on Central Nervous System: Basis for Rational Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **40**:125 (July) 1938; Action of Hypoglycemia on the Central Nervous System and the Problem of Schizophrenia from the Physiologic Point of View, J. A. M. A. **110**:1433 (April 30) 1938.

12. Himwich, H. E.; Frostig, J. P.; Fazekas, J. F., and Hadidian, Z.: Mechanism of the Symptoms of Insulin Hypoglycemia, Am. J. Psychiat. **96**:371 (Sept.) 1939.

13. Davis, P. A.: Effect on the Electroencephalogram of Changing the Blood Sugar Level, Arch. Neurol. & Psychiat. **49**:186 (Feb.) 1943.

14. Finesinger, J. E.; Lindemann, E.; Brazier, M. A. B., and Chapple, E. D.: Effect of Anoxia as Measured by Electroencephalogram and the Interaction Chronogram on Psychoneurotic Patients, Am. J. Psychiat. **103**:738 (May) 1947.

15. Brazier, M. A. B.; Finesinger, J. E., and Schwab, R. S.: Characteristics of Normal Electroencephalogram: Effect of Varying Blood Sugar Levels on the Occipital Cortical Potentials in Adults During Hyperventilation, J. Clin. Invest. **23**:319 (May) 1944.

16. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559 (Nov.) 1937.

17. Hoagland, H.; Cameron, D. E., and Rubin, M. A.: Electroencephalogram of Schizophrenics During Insulin Treatments: "Delta Index" as Clinical Measure, Am. J. Psychiat. **94**:183 (July) 1937.

in alpha wave frequency during insulin hypoglycemia in schizophrenic patients, suggesting that alpha activity is directly proportional to the rate of carbohydrate metabolism. Normal alpha activity disappears as cortical functions are repressed and reappears with restoration of cortical function by the administration of glucose. The same relationship appears with oxygen consumption. Himwich and associates [18] showed the disappearance of normal electroencephalographic rhythm as oxygen consumption decreased during hypoglycemia.

We wish to report four cases of neurological complication following insulin coma therapy, in three of which serial electroencephalographic studies were made.

REPORT OF CASES

Case 1.—E. W., a white man aged 32, divorced, was admitted to this hospital in October 1949. The patient had been "nervous" and absent-minded since his discharge from the Army, in 1942. Early in 1943 he was hospitalized elsewhere and during this period was emotionally regressed, disoriented, hallucinated, childish and indifferent. A diagnosis of hebephrenic schizophrenia was made. He had a spontaneous remission and was discharged in July 1943. He then made a good adjustment, finding steady employment as a fireman in steel mills, until his marriage in 1945. There ensued a long period of marital discord, until 1948, when the patient and his wife were separated and he returned to live with his mother.

The patient became more and more delusional, hyperactive and hallucinated, until it became impossible to manage him at home and he was brought to this hospital.

The patient was the third of six siblings. The father was a chronic alcoholic, and the family was held together by the mother, who was an overprotective and domineering person. One of the patient's siblings has been in a state hospital since 1938 with a condition diagnosed as schizophrenia. The patient was a shy, withdrawn boy, who always felt ill at ease outside the family setting. He finished nine grades of school and was an average student. He had always been in good health. There was no history of head injury, fainting spells, convulsions, alcoholism or fevers of undetermined origin.

On admission to the hospital, the patient was hyperactive, hypertalkative and inaccessible. He was hallucinatory, impulsive and delusional. Physical examination revealed nothing abnormal except mild malnutrition. The neurological status was within normal limits. The urine was normal; the blood cell count was normal; serologic reactions of the blood were negative, and a fasting blood glucose was 68.8 mg. per 100 cc. The roentgenogram of the chest showed nothing abnormal, and the electrocardiogram was normal.

The patient was placed on electric shock therapy on Oct. 28, 1949 and received a course of 15 treatments on a schedule of three treatments per week. During this period he showed considerable improvement, becoming less tense and more accessible, although he remained somewhat withdrawn. This improvement, however, was not maintained, and his overtly psychotic behavior appeared again. Electric shock therapy was begun once more, and after three treatments the patient showed improvement; he was then maintained on a schedule of one treatment a week until he had received a total of 10 treatments. A good remission ensued, but improvement was not maintained. It was then decided to give the patient insulin shock therapy, in an effort to establish the remission that he showed after each course of electric shock therapy.

Insulin coma therapy was started approximately three weeks after the last electric shock treatment. He was started on insulin sensitivity routine, being given an initial dose of 5 units of regular insulin, with increments of 5 units a day to a total of 25 units. The dose was then doubled each day, according to the method described by Shirley and Bond,[19] until the patient

18. Himwich, H. E.; Hadidian, Z.; Fazekas, J. F., and Hoagland, H.: Cerebral Metabolism and Electrical Activity During Insulin Hypoglycemia in Man, Am. J. Physiol. **125**:578 (March) 1939.

19. Shirley, J. T., and Bond, E. D.: Insulin Shock Therapy in Schizophrenia, Veterans Administration Technical Bulletin 10-501, Washington, D. C., 1948.

went into stage III coma, which occurred at a dose of 400 units, on the eighth treatment day. He was subsequently stabilized on a dose of 115 units over the subsequent 14 treatment periods. During this time nothing unusual was noted in the coma patterns. The patient usually went into stage III coma at 8:30 to 9:00 a. m. and had about one hour of deep coma (stages III and IV) a day. On the twenty-second treatment day he seemed to have more respiratory difficulty than usual, although no abnormality was noted after treatment. The insulin dose, however, was reduced from 150 to 100 units, and the following day to 80 units. On the twenty-fourth treatment day, on a dosage of 80 units, the patient was declared in stage III coma at 8:35 a. m. and was kept in coma one hour. His temperature during the coma period was 98 F. (rectal). On being awakened by intravenous injection of 12 Gm. of 25 per cent glucose solution, he seemed very restless, tossing about in bed, and appeared bewildered and confused. This was different from his usual quick return to consciousness. He was able to drink three cups of orange juice, however; but it was observed that he had poor coordination with his right hand and arm, and on examination his right hand and arm were found to be weak.

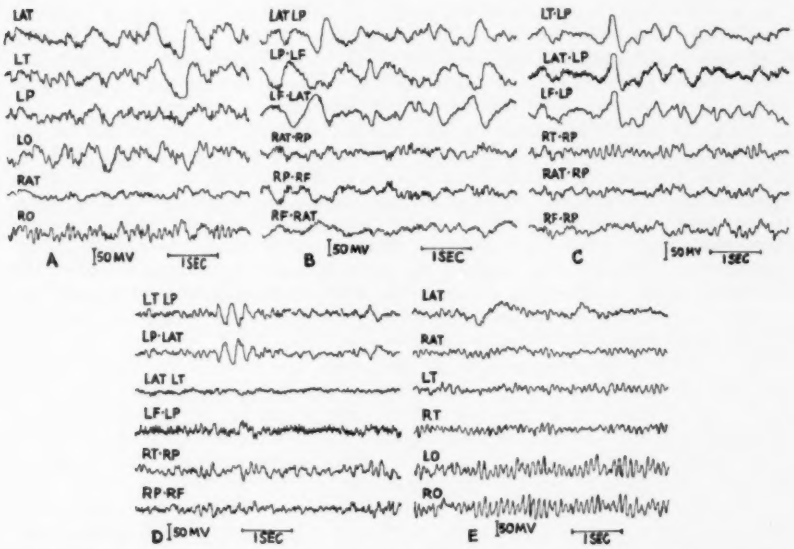


Fig. 1.—Electroencephalograms in case 1. In this figure and in figure 2, *AT* indicates record from the anterior temporal area; *T*, from the temporal area; *P*, from the parietal area; *O*, from the occipital area; *F*, from the frontal area, and *PT*, from the parietal and temporal areas.

Neurological examination revealed diminished reflexes of the right upper extremity. No pathological reflexes were elicited. The patient could not speak, although he could understand and carry out commands. He made efforts at communication, and these consisted of blowing and whistling.

The patient at this time received 100 cc. of 25 per cent glucose solution. The blood sugar prior to this injection was 65.9 mg. per 100 cc. The electroencephalogram taken at this time (fig. 1 *A*) showed a slow wave focus with many 2 to 3 per second waves of high amplitude over the entire left cortex, being most prominent in the left parietal and temporal leads. Diffuse 4 to 5 per second waves of voltage averaging about 50 millivolts were present over the entire left cortex. The right cortex showed an 8 per second basic frequency with infrequent short bursts of 5 per second waves of moderate voltage. About five hours after the aphasia was

first noted in the treatment ward, the patient was able to say "O" and "K" after some practice with the examiner. On April 5, 24 hours later, the two upper extremities were approximately equal in strength. The patient could then readily say simple phrases but still had difficulty in repeating the more complex sentence. He could repeat it if phrases were given him but got it jumbled up when he tried the full sentence. The patient had eaten well and had taken part in ward activities. The electroencephalogram (fig. 1 *B*) taken at this time showed no particular change. The blood sugar at the time of this recording (24 hours after onset of symptoms) was 156 mg. per 100 cc.

The following morning, 48 hours after onset, no abnormality in his speech was observable, and the patient could express himself without difficulty. There were no motor weaknesses, and the neurological status was normal. The electroencephalogram (fig. 1 *C*) taken that afternoon still showed a 2 to 3 per second, slow wave focus over the left hemisphere. The following day some improvement in the electroencephalogram was found (fig. 1 *D*). An average frequency of 7 per second was obtained in all leads, with only rare bursts of 4 per second waves of moderate voltage. On April 9, five days after the complication, the electroencephalogram (fig. 1 *E*) showed a fairly normal alpha pattern of 9 per second.

Case 2.—W. D., a white man aged 27, single, was admitted to this hospital in September 1948. He had been ill since his discharge from the Army, in 1947, and complained of irritability, "nervousness" and restlessness. He would have periods of great anxiety and confusion, lasting several days at a time, in which he was belligerent, accusatory and negativistic. On several occasions he became violent and struck his mother, with whom he was living.

The patient was the younger of two sons. He was very close to his father and felt that his mother always preferred his older brother to himself. The father died suddenly while the patient was in the service. The patient's early adjustment with other children and at school seemed to have been adequate. He completed high school one year before entering the Army. He had always been in good health, and there was no history of head injury, black-outs, convulsions or fever of undetermined origin. When the patient entered the hospital, he was cooperative and pleasant. He expressed the paranoid idea that his mother wished him hospitalized to prevent him from getting money which he believed belonged to him. He expressed ideas of reference and said he had noticed a strange happening in his neighborhood which made him believe that he had been drugged.

The results of physical and neurological examinations were normal. The urinary findings and blood cell count were within normal limits. Serologic reactions of the blood were negative; the fasting blood glucose measured 82.8 mg. per 100 cc., and a roentgenogram of the chest and spine revealed nothing abnormal. The electrocardiogram was normal. Electroencephalograms, obtained on Jan. 13 and Feb. 7, 1949, consisted of an over-all 9 per second frequency. No breakdown occurred after two minutes of hyperventilation.

The patient was started on insulin coma therapy on Dec. 9, 1948, in the usual manner. Early stage III coma occurred with a dose of 500 units of insulin on the tenth treatment day. Stabilization was obtained on a dose of 250 to 280 units. This was maintained until insulin resistance became pronounced, at approximately the forty-fifth treatment day. The dose was raised to 300 units because the patient was going into coma late in the morning. Coincident with this resistance, it was noticed that his temperature would rise to 100 or 100.8 F. (rectal) during the coma periods, whereas previously his temperature had remained in the range of 98 to 99 F. rectally. The dose of insulin was increased to 550 units, and on the sixty-second treatment day, after 54 hours of deep coma (stages III and IV), the patient was declared in coma at 9:45 a. m. Routine temperature determinations, which were made at 15 minute intervals, revealed that the patient had a sudden rise of temperature to 105 F. at 10:00 a. m. Coma was therefore terminated immediately. He was given 12 Gm. of dextrose intravenously, followed by oral administration of orange juice with 25 per cent solution of dextrose. The patient responded readily; but it was noticed that he had paralysis of the left side of the face, and examination revealed complete left hemiparesis and left hemianesthesia. The sensory changes consisted of loss of discrimination, proprioception and stereognosis. No abnormal signs referable to the pyramidal tract were elicited. He was fully awake and oriented at this

time. A continuous electroencephalographic recording was started at noon, and at this time the blood sugar level was 82 mg. per 100 cc. He was given 50 cc. of 50 per cent dextrose at 12:10 p. m., and then at 12:30 p. m., at approximately 20 minute intervals, he received, in order, 75 mg. of nicotinic acid, 5 cc. of nikethamide and 100 mg. of thiamine hydrochloride. At approximately 1:40 p. m. he again received 50 cc. of 50 per cent glucose intravenously. The electroencephalogram maintained its same abnormal appearance (fig. 2 *A*). There was an over-all basic frequency of 8 per second over the entire left hemisphere. The basic rhythm of the right hemisphere varied around a frequency 6 per second. The right hemisphere, especially over the parietal and temporal areas, revealed a focus of 2 per second rolling waves of high voltage. The patient returned to his ward, and gradual improvement was noted. The hemiparesis disappeared first, before the hemianesthesia, with complete recovery 10 hours after the onset. The following day the electroencephalogram was within normal limits, with a basic frequency of 8 per second in all leads (fig. 2 *B*).

CASE 3.—A. W., a single white man, was admitted to this hospital in January 1949. His illness apparently started in November 1948, while working in a lumber camp in California. He expressed many ideas of reference and feared death by castration. In an effort to get away from those he felt were persecuting him, he came east and was finally hospitalized here through the efforts of his brother. He had graduated from high school and then studied forestry in a college. He had worked in lumber camps both prior to and after military service. He served

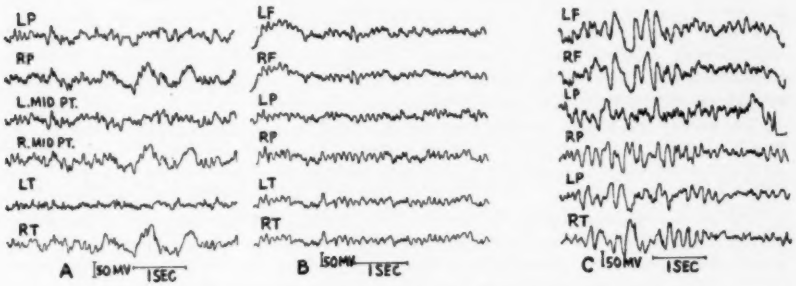


Fig. 2.—Electroencephalograms (*A* and *B*) in case 2 and (*C*) in case 3.

as a gunner in the air forces from 1941 to 1945 and at one time was grounded because of "combat fatigue." There was no record of serious illness or injury prior to or during service. His parents were living and well. He had two sisters, both of whom were married. There was no history of nervous or mental disease in any member of the family.

The patient had always been considered a seclusive, shy, sensitive person. On admission he was cooperative but somewhat suspicious. There was flattening of affect. He smiled quizzically and related his doubt as to whether or not people were really after him. The diagnosis was acute schizophrenic reaction, paranoid type.

Physical and neurological examinations revealed an essentially normal condition. The fasting blood sugar was 87.6 mg., and the nonprotein nitrogen 47.6 mg. Serologic reactions were negative, and the blood cell count and urine were within normal limits. An electroencephalogram taken January 26 showed a basic frequency of 9 per second, no focus, no paroxysmal discharges and no build-up with hyperventilation. The impression was that of a normal pattern.

He was placed on subcoma insulin therapy on Jan. 26, 1949, with an initial dose of 5 units and increments of 5 units each subsequent day until he received a dose of 80 units, on February 12. The following day he was placed in the insulin treatment ward and given regular insulin, 100 units. The highest dose of regular insulin he ever received was 150 units. During this period he was in coma 11¾ hours in stages III and IV. On the fourteenth

day of treatment he received 100 units of regular insulin and was in coma one hour (stages III and IV), without any significant changes in blood pressure, pulse or temperature. He was then given 12 Gm. of 25 per cent dextrose solution intravenously at 9:20 a. m., followed by 50 Gm. of dextrose in orange juice orally. On recovery he appeared his usual self, was helped in taking his shower and then walked into the dining room. While he was at the breakfast table, at 10:00 a. m., it was noticed that he had weakness of his right upper extremity. He refused to eat his breakfast at that time. His speech was coherent, with no evidence of any defect. Neurological examination revealed diminished biceps and triceps reflexes of the right arm with a positive Hoffmann sign. An electroencephalogram (fig. 2*C*) was immediately obtained, revealing a basic frequency of 6 per second in both hemispheres with frequent bursts of 3 to 4 per second waves of higher amplitude. Fifty cubic centimeters of 50 per cent glucose solution was given at 10:30 a. m., without any change in the record. At half-hour intervals he was given 5 cc. of nikethamide intravenously and then 100 mg. of thiamine hydrochloride, without any appreciable change in the electroencephalogram. Throughout the testing the patient was cooperative, being fully awake and oriented and without evidence of aphasia. He was returned to the ward, had a full lunch and later that afternoon spent some time with visitors. Repeated observations, both subjective and objective, revealed a fairly complete return of function of the right upper extremity, and at 5:00 p. m. neurological examination showed an essentially normal status. Unfortunately, a follow-up electroencephalogram was not obtained in this case.

Case 4.—A. F., a single white man aged 22, entered the neurological service of this hospital for investigation of severe headaches, of approximately one year's duration. The patient had seen many physicians before coming here and had been told that his trouble was his "nerves." The patient's condition was first evaluated on the neurological service, and he was then transferred to the psychiatric service, where a diagnosis of paranoid schizophrenia was made and he was recommended for insulin therapy.

The patient had always been in good health except for varicose veins, for which he had received surgical treatment, and a nasal obstruction. He had strained his back while in the service and continued to complain of occasional back pain. There was no history of head injury, loss of consciousness, seizures, fainting attacks or fever of undetermined origin.

The patient was preoccupied with thoughts about himself and had many somatic complaints with paranoid trends. He was tense and ill at ease. The findings on physical and neurological examinations were within normal limits. Roentgenograms of the chest, skull and spine were normal. The electrocardiogram was normal. The urine was normal; the blood cell count, normal, and the fasting blood sugar, 74.9 and 77.1 mg. per 100 cc. The electroencephalogram revealed a rhythmic record with a normal alpha pattern of 10 per second frequency throughout. The patient was started on subcoma insulin therapy because of his extreme anxiety. The initial dose of 40 units was increased 10 units a day, to a maximum dose of 130 units, over a period of approximately three weeks, including 13 treatment days. It was then decided to give the patient deep coma therapy. He was resistive to insulin and required 750 units of regular insulin before he went into stage III coma, on the twenty-fifth treatment day. In the next five treatment days, he had a total of 2¼ coma hours, with individual doses of insulin ranging from 375 to 500 units.

On November 13, the thirty-first treatment day, the patient received 600 units of insulin at 5:00 a. m. He was declared in stage III coma at 9:50 a. m. He awakened spontaneously and was given 37 Gm. of dextrose in orange juice at 10:45 a. m. after an uncomplicated coma period, without elevation of temperature or notable changes in pulse or blood pressure. He did not respond well and at 11:00 a. m. was given 25 Gm. of 25 per cent dextrose intravenously. He awoke very slowly and was cloudy and confused. It was noticed then that he had paralysis of the right lower side of the face, paralysis of the right upper extremity and motor aphasia. Reflexes of the right upper extremity were diminished. No pathological reflexes were noted.

At 11:15 a. m. he was given 25 Gm. of dextrose by vein. He responded slowly to commands. Verbalization was stereotyped, his response being "Yes, yes," to all questions. At 12:20 p. m. he was given 100 mg. of thiamine hydrochloride and 25 Gm. of dextrose intravenously. Efforts to speak brought only monosyllables or unintelligible mutterings. Nevertheless, he was alert

and cooperative. An electroencephalogram obtained at this time revealed the following pattern: The entire left hemisphere showed a basic rhythm of 6 per second frequency and moderate voltage. Interspersed in the activity on this side were some large rolling waves of 1 to 2 per second frequency. No sleep pattern was noted. The right hemisphere showed a normal alpha rhythm with a frequency of 9 per second. Orange juice with added dextrose was given to him at intervals. At 3:45 p. m. speech was slow and still somewhat unintelligible. A spinal tap revealed that the fluid was under normal pressure, with no cells and 121 mg. of sugar and 48.6 mg. of total protein, per 100 cc. By 6:00 p. m. of the same day he was able to answer questions more clearly. There was then no evidence of paralysis of the face and arm. Neurological examination revealed very slight weakness of the involved side. The next morning the patient offered no complaints, and the neurological status was normal. An electroencephalogram at this time showed a basic normal alpha rhythm of 9 per second frequency on both sides. There were a few random slow waves of 5 per second frequency over the left hemisphere. The record was considered to be within normal limits.

COMMENT

In a continuous series of 184 cases in which insulin coma therapy has been given at this hospital since 1946, reversible neurological complications developed in the four cases reported. In three cases there occurred paresis of the right upper extremity, and in two of these aphasia was present. In the other case paralysis of the left side of the face, left hemiparesis and left hemianesthesia were present. These findings appeared immediately on or shortly after administration of dextrose and return to consciousness and were transitory, the shortest duration being seven hours and the longest 48 hours. The transitory sensory disorders, such as paresthesias and visual disturbances, were commonly seen but were so fleeting that they were not recorded and are not considered here. Likewise, the other recognized complications of insulin coma, such as convulsive seizures and prolonged coma, have not been made a part of this study. In none of these cases was there any clinical or laboratory evidence to forewarn one of the impending complication. In one case a distinct rise in temperature did occur, necessitating termination of coma, after which the neurological complication appeared. This febrile reaction is not thought to have been specifically related.

The clinical findings presented here indicate involvement of the "higher," and functionally more complex, areas of the central nervous system, substantiating the observations of Hoefer [2b] on the greater susceptibility to low blood sugar of more complex and phylogenetically more recent areas of the brain.

The electroencephalograms were obtained with a Grass six channel machine, using monopolar and bipolar leads. In these four cases one or more normal brain wave tracings were obtained prior to the patient's receiving insulin coma treatment. As soon as possible after discovery of the complication, electroencephalographic tracings were obtained. All the patients received ample dextrose by mouth or vein to insure a blood sugar level which would not of itself influence the brain wave pattern. All the patients at the time of the recordings were fully awake and without any evidence of disturbance in consciousness. Electroencephalographic recordings were repeated at intervals, when possible, until a return to a normal pattern was obtained. The electroencephalographic tracings taken immediately after the complication was noted revealed an asymmetrical delta wave focus in three cases (E. W., fig. 1 *A*; W. D., fig. 2 *A*, and A. F.). In one case (A. W., fig. 2 *C*) diffuse bursts of delta activity appeared over both hemispheres; the reason for this peculiarity remains

unexplained. The asymmetrical abnormality persisted longest in case 1 (fig. 1 *B* and *C*), lasting three days, and lagged considerably behind the clinical improvement he showed. This patient, however, also had the slowest return of function. It may be pointed out that all the other patients had received thiamine hydrochloride, and some, in addition, had nikethamide and nicotinic acid. These drugs, however, produced no immediate recognizable improvement in the neurological abnormalities or the electroencephalographic tracings. Theoretically, thiamine, as the cocarboxylase in the enzyme system of carbohydrate metabolism, may stimulate the utilization of available glucose [19] and thereby bring about the more rapid improvement noted.

CONCLUSIONS

The occurrence of reversible neurological complications is apparently not as infrequent as has been supposed. The overlooking of a minimal paresis or other transitory neurological symptom is quite possible. Whenever there is a question of such a complication, an electroencephalogram may aid in establishing the disturbance in cerebral function.

In three of four cases, a focal electroencephalographic pattern was obtained and the site of abnormality corresponded to that of the anatomic area as determined by the neurological findings.

BABINSKI REFLEX AND MARIE-FOIX FLEXOR WITHDRAWAL REFLEX

Historical Notes

ROBERT WARTENBERG, M.D.
SAN FRANCISCO

THE HISTORY of neurology recounts many dramatic instances in which identical discoveries of significance have been made by two men independently. The discoverers did or did not live in the same country; the discoveries were made simultaneously or after an interval of many years. Exophthalmic goiter, for instance, was first adequately described by the Irishman Graves, in 1835, and by the German Basedow, in 1840. The clinical picture of adiposogenital dystrophy was outlined by the Frenchman Babinski, in 1900, and by the Austrian Fröhlich in 1901. The Russian Bechterew and the German Mendel both described the reflex of toe flexion elicited on tapping the dorsum of the foot in the year 1904. Epidural injection was reported before the Société de Biologie de Paris on April 20, 1901 by Sicard and at a later meeting, on April 27, 1901, by Cathelin. Chordotomy for the relief of pain was introduced by the Americans Spiller and Martin in 1912 and by the German Foerster in 1913. An Austrian, Schüller, reported the displacement of the calcified pineal gland in 1912; the American Naffziger reported on the "pineal shift" in 1926. The test for pain on jugular compression was performed by the Swede Landelius in 1926 and reported by Naffziger and Jones in 1935. The first paper on neuritis of the lateral cutaneous nerve of the thigh (meralgia paresthetica), written by the German Bernhardt, appeared on March 15, 1895, and the monograph of the Russian Roth (who coined the name meralgia paresthetica), on April 1 of the same year. The American Dandy described encephalography via lumbar puncture in 1918; the German Bingel, in 1923. The New Yorker Rosett described the hyperventilation test in 1924; the German Foerster did it in the same year (and not in 1926, as Wilson states). Lumbar puncture is usually associated with the work of the German Quincke, in 1891, but this puncture was performed by the New Yorker Corning two years earlier. The famous sign of Tinel, "distant tingling on percussion," is based on an article by him which appeared in a French journal on Oct. 7, 1915. The very same phenomenon, however, had been described by Paul Hoffmann in a German medical periodical in the issue of March 28 of the same year. The Germans, therefore, speak of the Hoffmann-Tinel sign. Loss of the patellar reflex in tabes was reported in 1875 independently by Westphal and by Erb. Dagnini described slowing of the pulse following pressure on the eyeball—now called Aschner's phenomenon—in June 1908, whereas Aschner described it in October 1908. The Frenchmen Weill and Reys stressed the association of pupillotonia with the loss of reflexes in 1926, five years before Adie. Gonda mentioned

From the Division of Neurology, University of California School of Medicine.

his reflex briefly in 1941 and described it in 1942, but the Rumanian Grigorescu had reported in detail on exactly the same reflex in 1940. In some of these cases ugly and fruitless controversies regarding priority ensued. But in most of them credit was given—albeit belatedly—to the first discoverer.

BABINSKI REFLEX

The history of the Babinski reflex and the Marie-Foix flexor withdrawal reflex is remarkable in that the first describers of these phenomena have been almost completely forgotten. If anyone should say that the Babinski reflex, isolated dorsiflexion of the big toe on stimulation of the foot, had been described before Babinski, it would seem highly incredible. However, the inexorable facts are these: Babinski [1] reported on his reflex at the meeting of the Société de Biologie de Paris, Feb. 22, 1896. The German neurologist E. Remak (1848-1911) presented a patient with myelitis dorsalis transversa before the Berlin Society for Psychiatry and Nervous Diseases, July 10, 1893. In an article entitled, "On the Localization of the Spinal Skin Reflexes of the Lower Extremities," which is based on this demonstration and was published in 1893,[2] Remak said, verbatim:

Zunächst gelingt es durch kurzes Streichen an der distalen Hälfte der Plantarseite des Metatarsus primus einen ziemlich isolirten Reflex des Extensor hallucis longus zu produciren. [First of all one is able, through short stroking on the distal half of the plantar aspect of the metatarsus primus, to evoke a fairly isolated reflex of the extensor hallucis longus.]

Remak did not elaborate further on his primary observation. He found this isolated dorsiflexion of the big toe on stroking the sole of the foot in a 4 year old boy with transverse myelitis, at the level below the seventh thoracic segment. In this case Remak was concerned particularly with his "femoral reflex." This held his entire attention, and he referred to it later.[3] In this later article, too, the femoral reflex again captured his attention at the expense of other clinical phenomena observed. This reflex consisted of plantar flexion of the first three toes, plantar flexion of the foot and extension of the knee on stimulation of the inner aspect of the thigh. This reflex, which physiologically is the homolateral mass extension reflex, did not prove to be of any great clinical significance.

Six years later, and three years after Babinski had described his own reflex (1896), Remak [4] himself pointed out (1899) that he had described this isolated reflex of the extensor hallucis longus on stimulation of the sole of the foot in 1893. But he said that at that time he did not know that this reflex, as such, was a pathologic one. Indeed, he paid so little attention to this observation that in the "Proceedings of the Berlin Society for Psychiatry and Nervous Diseases" of July

1. Babinski, J.: Sur le réflexe cutané plantaire dans certaines affections organiques du système nerveux central, Compt. rend. Soc. biol. **3**:207-208, 1896.

2. Remak, E.: Zur Localisation der spinalen Hautreflexe der Unterextremitäten, Neurol. Centralbl. **12**:506-512 (Aug. 1) 1893.

3. Remak, E.: Über den "Femoralreflex" bei Leitungsstörung des Dorsalmarks, Neurol. Centralbl. **19**:7-9 (Jan. 1) 1900.

4. Remak, in discussion on Koenig, W.: Über die bei Reizung der Fussohle zu beobachtenden Reflexerscheinungen mit besonderer Berücksichtigung der Zehenreflexe bei den verschiedenen Formen der cerebralen Kinderlähmung. Neurol. Centralbl. **18**:612 (July 1) 1899.

10, 1893,[5] this observation is not even mentioned and only the femoral reflex is reported. It was Babinski who realized the clinical importance and the pathologic significance of the reflex. Apparently, not until 1904 did Babinski[6] mention the observation of Remak; otherwise, this seemed to have remained completely unnoticed. It is not mentioned in the very complete historical review on the Babinski sign by Lewy.[7]

This minor intermezzo, of course, does not detract from the historic importance of the report made by Babinski[1] at the meeting of the Société de Biologie de Paris on Feb. 22, 1896, when he described his phenomenon, three years after Remak. It only proves how right was James Russell Lowell when he once said, "It is not the finding of a thing, but the making something out of it after it is found, that is of consequence"; or, as Osler put it, "In science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs."

FLEXOR WITHDRAWAL REFLEX

The clinically and physiologically very significant flexor withdrawal reflex is usually attributed to Marie and Foix,[8] on the basis of their work done during the period 1910 to 1912. When positive, the reflex is characterized by flexion of the leg in all joints on passive flexion of the toes. This is called the Marie-Foix maneuver. However, von Bechterew[9] described the same phenomenon in 1906, four years before Marie and Foix. Later, in 1927,[10] he stressed his priority for the discovery of this phenomenon. Physiologists and clinicians did a great amount of work on this phenomenon, always referred to as the Marie-Foix, or, less commonly, the Bechterew-Marie-Foix, maneuver. But in the vast literature on this and allied clinical phenomena, nowhere is there mentioned the name of the American neurologist who adequately described this phenomenon long before either Bechterew or Marie and Foix, i. e., in 1888. This was done by Wharton Sinkler,[11] the Philadelphia neurologist and former assistant of S. Weir Mitchell. Sinkler was born in 1845 (not in 1847, as Kelly states in his "Encyclopedia") and died in 1910. In 1891 he was president of the American Neurological Association. In an article entitled, "The Toe Reflex," published in 1888,[11] Sinkler described a reflex

5. Remak, E.: Zur Localisation der spinalen Hautreflexe der Unterextremitäten, Berl. klin. Wchnschr. **31**:98 (Jan. 22) 1894.

6. Babinski, J.: Sur la transformation du régime des réflexes cutanés dans les affections du système pyramidal, Rev. neurol. **12**:58-62 (Jan. 30) 1904.

7. Lewy, F. H.: Das Babinskische und verwandte Phänomene, Monatsschr. Psychiat. u. Neurol. **25**:56-70, 1909.

8. Marie, P., and Foix, C.: Sur le retrait réflexe du membre inférieur provoqué par la fléxion forcée des orteils, Rev. neurol. **20**:121-123 (July 30) 1910; les réflexes d'automatisme médullaire et le phénomène des raccourcisseurs: leur valeur sémiologiques, leur signification physiologique, ibid. **20**:657-676 (May 30) 1912.

9. von Bechterew, W.: Über eine eigentümliche Reflexerscheinung bei Plantarflexion des Fusses un der Zehen in Fällen von Affektion des centralen motorischen Neurons, Neurol. Centralbl. **25**:290-291 (April 1) 1906.

10. von Bechterew, W.: Über komplizierte Reflexerscheinungen bei Affektion des zentralen motorischen Neurons, Ztschr. ges. Neurol. u. Psychiat. **108**:41-55, 1927.

11. Sinkler, W.: The Toe Reflex, Med. News **53**:611-612 (Dec. 1) 1888.

which he, two years previously, had demonstrated at a meeting of the Philadelphia Neurological Society. The reflex is described as follows:

> The patient lying on his back with his legs extended, the observer grasps the great toe and flexes it strongly; there immediately follows involuntary flexion of the foot, then flexion of the leg occurs, and lastly, the thigh is flexed on the pelvis.

On this basis, the historian Garrison [12] states: "Wharton Sinkler isolated the great toe reflex, 1888." This statement is incomplete, and therefore somewhat confusing, for later in his text Sinkler says: "Flexing of all of the toes at the same time causes the same result." Referring to a case which showed "complete paralysis of motion and sensation below the sixth dorsal vertebra," and in which there evidently was a transverse lesion of the spinal cord with concomitant spastic phenomena in the lower extremities, Sinkler says: "On flexing the toes, either the great toe alone or all of the toes together, the foot is quickly and strongly flexed, then the leg is drawn up, and finally the thigh is flexed on the abdomen." There is the flexor withdrawal reflex, plain and simple, and if any name at all should be attached to the "flexor withdrawal reflex," it should be that of Sinkler. It was he who described this reflex 18 years before Bechterew and 22 years before Marie and Foix. The amazing fact is that neither of these authors ever mentioned Sinkler's work.

In 1913 Strohl,[13] a pupil of Pierre Marie, at his suggestion, wrote an exhaustive monograph on the reflexes of medullary automatism, based on clinical material from Pierre Marie's service at Salpêtrière. The French, German, Belgian, Russian, Italian and Dutch literature is cited abundantly here, as far back as 1667. There are 130 references. But not a word about Sinkler. The European authors have apparently been influenced by what H. L. Mencken calls "the famous sneer" of Sydney Smith, who wrote in 1820: "In the four quarters of the globe, who reads an American book? . . . What does the world yet owe to American physicians or surgeons?"

---

12. Garrison, F. H.: An Introduction to the History of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1929, p. 644.

13. Strohl, A.: Les réflexes d'automatisme médullaire, Paris, G. Steinheil, 1913.

GLUCOSE TOLERANCE IN CHRONIC SCHIZOPHRENIA AND SENILE STATES

WERNER SIMON, M.D.
AND
JAMES T. GARVEY, M.D.
MINNEAPOLIS

ABNORMAL glucose tolerance, characterized by a reduction of the tolerance to ingested sugar, has been reported in various mental disorders by a number of investigators. Diabetic-like blood sugar curves of a sustained type have been found in cases of schizophrenia, indicating a biochemical disturbance of the carbohydrate metabolism in this condition. Meduna and Vaichulis [1] reported diabetic-like reaction to the Exton-Rose glucose tolerance test in about 60 per cent of unselected schizophrenic patients. In a previous study, Meduna, Gerty and Urse [2] demonstrated a delay in the return of the blood sugar to a normal level following infusion of a dextrose solution in all of their 20 untreated schizophrenic patients. They concluded that a disturbance of the carbohydrate metabolism existed, as indicated by a delayed utilization of blood sugar, and postulated that this disturbance might be one of the etiologic factors in schizophrenia. However, Meduna, Braceland and Vaichulis [3] reported that the same type of abnormal curve can be obtained in the depressed and manic phases of manic-depressive psychosis and theorized that the same pathologic disturbance could be of etiologic significance in both schizophrenia and manic-depressive psychosis. Freeman, Rodnick, Shakow and Lebeaux [4] studied the carbohydrate tolerance of mentally disturbed soldiers and reported a reduction in glucose tolerance in two thirds, the dysfunction occurring not only in patients with schizophrenia but also in patients with nonpsychotic mental disturbances. They presented the hypothesis that reduced glucose tolerance is somehow related to emotional ten-

From the Neuropsychiatric Service, Veterans Administration Hospital, Minneapolis, and the Department of Psychiatry and Neurology, University of Minnesota.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Meduna, L. J., and Vaichulis, J. A.: A Hyperglycemic Factor in the Urine of So-Called Schizophrenics, Dis. Nerv. System **9**:248-250 (Aug.) 1948.

2. Meduna, L. J.; Gerty, F. J., and Urse, V. G.: Biochemical Disturbances in Mental Disorders: Anti-Insulin Effect of Blood in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **47**:38-52 (Jan.) 1942.

3. Meduna, L. J.; Braceland, F. J., and Vaichulis, J. A.: Diagnostic Difficulties and Levulose Tolerance Test in "Functional" Mental Diseases, Dis. Nerv. System **4**:101-114 (April) 1943.

4. Freeman, H.; Rodnick, E. H.; Shakow, D., and Lebeaux, T.: The Carbohydrate Tolerance of Mentally Disturbed Soldiers, Psychosom. Med. **6**:311-317 (Oct.) 1944.

sion. Freeman and Elmadjian [5] emphasized that the phenomenon is found in all phases of mental disease, especially in the acute phase. They stated the belief that the reduction in glucose tolerance is not specific for schizophrenia but, rather, is a response to a psychologic stress situation, since a normal glucose tolerance can be changed to a reduced tolerance in an experimental stress procedure. Proctor, Dewan and McNeel [6] studied glucose tolerance in schizophrenic patients after insulin shock therapy and found an improved mental status accompanied with an increase in glucose tolerance. Changes in glucose tolerance induced by electroshock therapy were studied by Freeman and Zaborenke [7] in 28 patients, 16 of whom had schizophrenia. They found a striking relation between emotional disturbance and sugar tolerance in individual patients, but in a majority of cases there was no remarkable correlation of the glucose tolerance and the degree of improvement. They concluded that reduced glucose tolerance seen in psychotic patients is due primarily to anxiety and emotional tension associated with the mental condition. In an earlier publication Freeman and Elmadjian [8] considered the relation of age and duration of hospitalization to abnormal glucose tolerance in psychotic patients and concluded that the duration of illness probably plays a more important role than does chronological age. Their abnormal group was somewhat older, and the question arose as to whether the response was in some way related to the aging process. On the other hand, these authors recognized that a long period of hospitalization, with considerable regression and withdrawal from stressful living, in the protective environment of the hospital, must result in lessening of tension.

Glucose tolerance in elderly patients has been studied by several authors. Hofstatter, Sonnenberg and Kountz [9] found no remarkably high rise in carbohydrate sensitivity in 154 subjects of an average age of 65. Horvath, Wisotsky and Corwin [10] noted a lack of consistency on repeated tests in the 60 to 70 year age group and concluded that on the average there is a slight but questionable diminution in tolerance. Deren [11] studied 50 patients over the age of 55 and found their fasting blood sugar normal but noted a prolonged upward trend of the blood sugar tolerance curves. He concluded that carbohydrate metabolism is impaired in old age. Marshall [12] found many variations in a group of 27 healthy men of an average age of 72.

---

5. Freeman, H., and Elmadjian, F.: Carbohydrate and Lymphoid Studies in Schizophrenia, Am. J. Psychiat. **9**:660-667 (March) 1950.

6. Proctor, L. D.; Dewan, J. G., and McNeel, B. H.: Variations in Glucose Tolerance Observations in Schizophrenics Before and After Shock Treatment, Am. J. Psychiat. **100**: 652-658 (March) 1944.

7. Freeman, H., and Zaborenke, R. N.: Relation of Changes in Carbohydrate Metabolism to Psychotic States, Arch. Neurol. & Psychiat. **61**:569-576 (May) 1949.

8. Freeman, H., and Elmadjian, F.: The Relationship Between Blood Sugar and Lymphocyte Levels in Normal and Psychotic Subjects, Psychosom. Med. **9**:226-232 (July-Aug.) 1947.

9. Hofstatter, L.; Sonnenberg, A., and Kountz, W. B.: Glucose Tolerance in Elderly Patients, Biol. Symposia **11**:87-95, 1945.

10. Horvath, S.; Wisotsky, R., and Corwin, W.: Oral Glucose Tolerance Test in Old Men, J. Gerontol. **2**:25-30 (Jan.) 1947.

11. Deren, M. D.: Dextrose Tolerance in the Aged, J. Lab. & Clin. Med. **22**:1138-1141 (Aug.) 1937.

12. Marshall, F. W.: Sugar-Content of the Blood in Elderly People, Quart. J. Med. **24**:257-284 (Jan.) 1931.

PRESENT INVESTIGATION

In order to study the problem of reduced glucose tolerance, we compared a group of patients with chronic schizophrenia with a group of patients with senile psychosis. Twenty-eight patients with chronic schizophrenia were selected, all of whom had been hospitalized between 15 and 25 years. There were 10 patients in the group with a senile psychosis. The age of the schizophrenic group ranged from 50 to 73; that of the senile group, from 64 to 86. The patients in both groups were in satisfactory physical condition. They all received the same diet for at least a week before

Results of Modified Exton-Rose Glucose Tolerance Test

Patient No.	Blood Sugar Level, Mg./100 Cc.			
	Fasting	30 Min.	60 Min.	120 Min.
	Patients with Chronic Schizophrenia (28)			
1.	82	133	175	154
2.	82	93	181	138
3.	92	140	116	106
4.	96	118	125	120
5.	76	136	144	120
6.	88	122	140	109
7.	82	106	94	76
8.	82	144	152	133
9.	109	140	133	112
10.	76	112	124	77
11.	76	120	169	144
12.	70	104	120	124
13.	67	97	112	116
14.	77	122	102	79
15.	57	112	148	133
16.	102	120	104	98
17.	77	98	125	118
18.	88	136	148	91
19.	70	100	82	72
20.	82	127	148	130
21.	96	135	144	130
22.	76	90	84	80
23.	74	133	136	157
24.	96	156	205	99
25.	64	93	102	97
26.	78	92	122	76
27.	64	86	99	49
28.	74	130	163	122
Mean values	80	118	132	109
	Senile Patients (10)			
1.	88	122	179	144
2.	94	152	174	144
3.	85	106	118	125
4.	85	133	148	99
5.	82	133	125	109
6.	100	144	152	122
7.	80	109	125	99
8.	82	129	133	72
9.	82	96	122	88
10.	68	133	208	169
Mean values	85	126	148	117

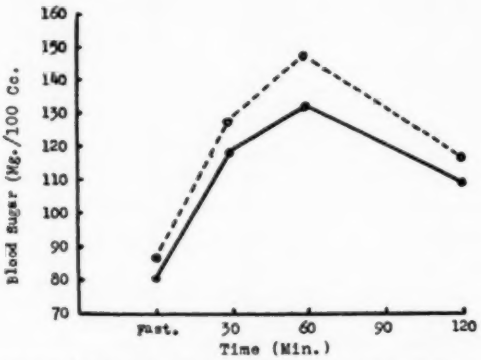
they were tested. Exercise and amount of rest were standardized prior to testing. Breakfast was omitted on the day of the test.

Method.—A modified Exton-Rose [13] technique was employed. Two doses of 50 Gm. of glucose dissolved in 250 cc. of water were given orally 30 minutes apart under fasting conditions. Samples of venous blood were drawn immediately before the ingestion of each administration of glucose and 30 minutes and 1½ hours after the second dose. The method therefore consisted of three blood samples taken during a period of one hour at 30 minute intervals and a fourth sample taken after an additional hour. A normal response is characterized by a rise in blood

13. Exton, W.; Rose, G., and Rose, A. R.: The One-Hour, Two-Dose Dextrose Tolerance Test, Am. J. Clin. Path. **4**:381-399 (Sept.) 1934.

sugar during the first 30 minutes and a decline or flattening of the curve after the second 30 minutes, with a return to normal, or even below the initial reading, after another 60 minutes. The blood sugar determinations were carried out with the Folin-Wu technique, the measurements being made by means of a photoelectric colorimeter.

Results.—Fasting blood sugar values for the schizophrenic group ranged from 57 to 109 mg. per 100 cc., with a mean of 80 mg. per 100 cc., and those for the senile group, from 68 to 100 mg. per 100 cc., with a mean value of 85 mg. per 100 cc. Of the patients with chronic schizophrenia, 67.9 per cent had abnormal, diabetic-like curves, whereas 80 per cent of the senile patients showed similar abnormal responses. One schizophrenic patient's blood sugar rose from a fasting reading of 96 mg. per 100 cc. to one of 205 mg. per 100 cc. after one hour, and one senile patient had corresponding readings of 68 and 208 mg. per 100 cc. These are extreme examples. The mean values for the two groups, when compared, reveal a somewhat higher fasting value (5 mg. per 100 cc.) for the senile group. The rise 30 minutes after ingestion of the first dose of glucose averaged 38 mg. per cent for the schizophrenic



Means obtained in a modified Exton-Rose glucose tolerance test on 28 patients with chronic schizophrenia (solid line) and 10 patients with senile psychosis (broken line).

group and 41 mg. per 100 cc. for the senile group. After ingestion of the second dose of glucose, the mean blood sugar values rose 14 mg. per 100 cc. for the schizophrenic group and 22 mg. per 100 cc. for the senile group. Two hours after the fasting blood sugar determination, the mean value for the schizophrenic group was 109 mg. per 100 cc.—29 mg. per 100 cc. higher than the initial reading, whereas the mean for the senile group was 117 mg. per cent—32 mg. per cent higher than at the onset of the test.

COMMENT

These findings indicate that the blood sugar, and with it the sugar metabolism, is more labile and disturbed in patients with a senile psychosis than in chronic schizophrenic patients. In percentages of abnormal responses (80 to 67.9 per cent), as well as in mean values, the senile patients appear to react in a more abnormal manner than the schizophrenic patients to the Exton-Rose blood sugar tolerance test. It has been stated that changes in glucose tolerance are found in all mental disorders and that this biochemical disturbance is related to stress predominant in

the acute phase of mental disease. However, the patients tested in this series had undergone a long period of hospitalization and had led a simple life in a protected environment, conducive to decreased tension and anxiety. It appears then that the abnormal glucose tolerance is related to the aging process, since the senile group showed more pronounced deviations in both number and type of response.

Fasting blood sugar values for schizophrenic patients usually are within normal limits (William Freeman [14]). In many patients, however, the blood sugar curve shows a continuous rise when the Exton-Rose two dose test is used. What attempts have been made to explain this abnormal response, which has been confirmed by a number of investigators? Is it due to an oversecretion of epinephrine, a reduced secretion of insulin, an inability to respond to the hormone, or to other endocrine disturbances?

Meduna and associates [2] stated that the explanation lies in an anti-insulin factor, which they believed to be present in 60 per cent of schizophrenic patients and which they felt could be tested biologically in experimental animals. It was their hypothesis that this factor is of pituitary origin. Since the carbohydrate metabolism is under the control of three glands (pancreas, adrenals and pituitary), the maintenance of the blood sugar level depends on a delicate balance and harmonious action of their hormones. Meduna believes that the diabetic-like sugar tolerance curves are due to delayed and diminished action of the insulin function, on the basis of hyperactivity of an anti-insulin factor, a product of the anterior lobe of the pituitary. In a more recent study,[1] Meduna and Vaichulis reported on a hyperglycemic factor in the urine of schizophrenic patients, which when injected intraperitoneally into rabbits increased their blood sugar markedly. They postulated a specific type of mental disorder characterized by pathologic carbohydrate metabolism, as indicated by a pseudodiabetic reaction to the Exton-Rose test, protracted sugar tolerance curves and the presence of an anti-insulin factor in the urine. Meduna named this disease oneirophrenia.

Goldner and Ricketts [15] attempted to repeat Meduna's experiments, but their results were not in agreement, and they failed to demonstrate the presence of a specific anti-insulin factor in the blood of schizophrenic patients. They found notable variations among their patients, as well as individual differences in the blood of the same patient from day to day.

The problem of insulin resistance in psychotic patients has been investigated by several authors, without uniform findings. Horvath and Friedman [16] gave schizophrenic patients intravenous injections of insulin and reported a delayed hypoglycemic effect. Gellhorn, Feldman and Allen [17] obtained an increase in blood insulin of psychotic patients with a hypoglycemic effect when the patients were under stress of excitement, but in the quiet state the insulin content did not differ from that of

14. Freeman, W.: Fasting Blood Sugar in Schizophrenia, Am. J. Med. Sc. **186**:621-630 (Nov.) 1933.

15. Goldner, M. G., and Ricketts, H. T.: Significance of Insulin Inhibition by Blood of Schizophrenic Patients, Arch. Neurol. & Psychiat. **48**:552-560 (Oct.) 1942.

16. Horvath, S. M., and Friedman, E.: The Effects of Large Doses of Intravenous Insulin in Psychotic Nondiabetic Patients, J. Clin. Endocrinol. **1**:960-966 (Dec.) 1941.

17. Gellhorn, E.; Feldman, J., and Allen, A.: Effect of Emotional Excitement on the Insulin Content of the Blood: Contribution to Physiology of Psychoses, Arch. Neurol. & Psychiat. **47**:234-244 (Feb.) 1942.

normal subjects. Freeman and associates [18] found that 41 per cent of their series of schizophrenic patients showed some degree of insulin resistance and a less rapid recovery from the hypoglycemic phase than did a normal control group. They found no relation to age, duration of hospitalization or subtype of schizophrenic psychosis. Their results are consistent with the findings of Meduna, Gerty and Urse [2] but are not in agreement with Gellhorn's theory of predominance of the vagoinsulin mechanism in schizophrenia. Considered in the light of autonomic imbalance, there appears to be predominant reactivity of the sympathicoadrenal mechanism, which may explain the insulin resistance in schizophrenic patients which occurs frequently during insulin shock therapy when extremely large doses become necessary to produce coma.

Mott [19] reported the adrenal glands of schizophrenic patients to be approximately half the size and weight of the normal gland. He observed no changes in the cortex, but the medulla showed smaller, vacuolated cells with poor staining qualities. Pincus and associates [20] found that adrenocortical response to stress is reduced in schizophrenic patients as compared with that of normal subjects. Freeman and Elmadjian [8] investigated the relation between dysfunction in sugar metabolism and reduced adrenal activity by measuring the variation in the absolute lymphocyte levels, utilizing the fact that discharge of adrenocortical hormone results in lymphopenia. They found a sluggish lymphopenic reaction to the ingestion of glucose in schizophrenic patients, which they believe indicates a less active adrenocortical response in this psychosis. They arrived at the hypothesis that the schizophrenic patient suffers from an adrenocortical deficiency and that in chronic cases there may be irreversible physiologic changes involving the lymphocyte-glucose relationship.

Forsham and Thorn [21] listed as one of the functions of the adrenal cortex increased utilization of both fat and protein, with a decreased utilization of carbohydrate. Adrenocortical hormones aid in the conservation of carbohydrate stores and in patients with Addison's disease increase liver glycogen and raise the concentration of blood sugar. The carbohydate-regulating action of the adrenal cortex is presumed to be for the purpose of making available at all times the reserves of liver glycogen. In this connection, it has been found that hyperglycemia due to diabetes has a beneficial effect on patients with Addison's disease.

In a more recent study, Freeman and Elmadjian [5] again investigated the relation of the adrenal cortex to carbohydrate metabolism in schizophrenic patients and concluded that in this disorder there are a reduction of tolerance to glucose and a deficient response of the adrenal cortex to stimulation through the ingestion of sugar. They offered the hypothesis that "emotional disturbances affect the adrenal cortex via the anterior pituitary to accelerate the breakdown of protein to produce an

18. Freeman, H.; Looney, J. M.; Hoskins, R. G., and Dyer, C. G.: Results of Insulin and Epinephrine Tolerance Tests in Schizophrenic Patients and in Normal Subjects, Arch. Neurol. & Psychiat. **49**:195-203 (Feb.) 1943.

19. Mott, cited by Meduna and others.[2]

20. Pincus, G.; Hoagland, H.; Freeman, H.; Elmadjian, F., and Romanoff, L. P.: A Study of Pituitary-Adrenocortical Function in Normal and Psychotic Men, Psychosom. Med. **11**:74-101 (March-April) 1949.

21. Forsham, P. H., and Thorn, G. W.: The Diagnosis and Treatment of Adrenal Cortical Insufficiency, Veterans Administration Technical Bulletin 10-62, Washington, D. C., March 1950.

excessive amount of glucose once the exciting mechanism is set by the ingestion of carbohydrate." These authors have found abnormal sugar tolerances as frequent in chronic as in acute schizophrenia but leave unanswered the question as to whether the phenomenon is due to primary deficiency or is the result of exhaustion following chronic overstimulation from severe emotional tension.

SUMMARY AND CONCLUSIONS

Twenty-eight patients with chronic schizophrenia were compared with 10 patients with senile psychosis and studied with a modified Exton-Rose glucose tolerance test.

Of the patients with chronic schizophrenia, 67.9 per cent showed abnormal, diabetic-like responses, as compared with 80 per cent of the group with senile psychosis.

The mean values for the two groups reveal a severer disturbance in the senile patients.

It appears that this biochemical disturbance is related not only to stress, tension and anxiety but also to the aging process.

A review and discussion of the literature concerning glucose tolerance in mental disorders is included.

POSTPARTUM NECROSIS OF THE ADENOHYPOPHYSIS WITH HYPOGLYCEMIC CONVULSIONS

EDWARD C. CLARK, M.D.
MURRAY FRANKLIN, M.D.
AND
ADOLPH L. SAHS, M.D.
IOWA CITY

THE FIRST adequate description of severe insufficiency of the anterior lobe of the pituitary gland was given in 1914 and later amplified by Simmonds,[1] who suggested that one of the causes was embolic necrosis occurring in a septic puerperium. However, it was not until Sheehan's series of classic papers [2] that the relation of the clinical syndrome to ischemic necrosis of the adenohypophysis, following severe postpartum collapse and hemorrhage, was clarified.

That hypoglycemia and associated convulsive seizures can occur in this disease first was suggested by J. Wilder in 1930, according to Farquharson.[3] Since convulsions may be the presenting symptom, this disorder is of considerable interest to the neurologist. In view of the increasing frequency with which the condition is being diagnosed, the following case report may be of value.

REPORT OF A CASE

On May 25, 1950, one of us (E. C. C.) was called to a neighboring town to see a patient (Mrs. F. H.) who was experiencing focal seizures in her left arm. Her history was furnished by her husband and mother, who could recall no similar illness in the family. The patient, they said, had been born 45 years before. Except for a congenitally dislocated right hip, she had been well until the delivery of her third child, by breech presentation, May 13, 1933. The labor was prolonged; the patient lost much blood and apparently was in shock. The child lived one day.

From the Department of Neurology (Dr. Clark and Dr. Sahs) and the Department of Internal Medicine (Dr. Franklin) State University of Iowa College of Medicine.

1. Simmonds, M.: Über Hypophysisschwund mit tödlichem Ausgang, Deutsche med. Wchnschr. **40**:322-323 (Feb. 12) 1914; Über embolische Prozesse in der Hypophysis, Arch. path. Anat. **217**:226-239 (Aug.) 1914; Atrophie des Hypophysisvorderlappens und hypophysäre Kachexie, Deutsche med. Wchnschr. **44**:852-854 (Aug. 1) 1918.

2. (*a*) Sheehan, H. L.: Post-Partum Necrosis of the Anterior Pituitary, J. Path. & Bact. **45**:189-214 (July) 1937. (*b*) Sheehan, H. L., and Murdoch, R.: Post-Partum Necrosis of the Anterior Pituitary: Pathological and Clinical Aspects, J. Obst. & Gynaec. Brit. Emp. **45**: 456-489 (June) 1938. (*c*) Sheehan, H. L.: Simmonds's Disease Due to Post-Partum Necrosis of the Anterior Pituitary, Quart. J. Med. **8**:277-309 (Oct.) 1939. (*d*) Sheehan, H. L., and Summers, V. K.: The Syndrome of Hypopituitarism, ibid. **18**:319-378 (Oct.) 1949.

3. Farquharson, R. F.: Simmonds' Disease: Extreme Insufficiency of the Adenohypophysis, Springfield, Ill., Charles C Thomas, Publisher, 1950.

After this episode the patient no longer menstruated. It was noted that she tired easily, became increasingly somnolent and lost all her sexual desire. Most of her eyebrows and eyelashes and all of her body hair gradually disappeared. The hair line of her forehead receded, and her face, hands and feet became puffy. On several occasions she was told by different physicians that she was anemic.

In 1947 she was examined by a local doctor, who prescribed thyroid extract for her. During the next 2½ years she apparently took the medicament very irregularly and in small doses. Except for the appearance of a few more hairs in her eyebrows and lashes, there was no change in her condition.

In July 1949 she experienced an episode of confusion, during which time she perspired a great deal. The attack lasted five hours and stopped shortly after she was given some wine to drink.

During the fall of 1949 the thyroid medication was discontinued by another physician. From time to time the patient complained of abdominal pain. Her speech became slurred, and she slept most of the day.

On May 21, 1950 she began to sweat a great deal and by May 25 was markedly confused. During the morning of that day she experienced several episodes of convulsive movements of the left arm, lost consciousness and continued to perspire.

Later in the morning she was admitted to a local hospital. Because increased intracranial pressure was considered a possibility, she was given 200 cc. of 10 per cent glucose solution intravenously. Shortly after this she regained consciousness and was able to talk to her family. However, in about an hour she had a general seizure and again lapsed into coma.

On physical examination, about two hours later, she was unconscious, with puffy face, hands and feet. There was no evidence of emaciation. Only a few hairs could be found in the pubic area and axillas and on the arms and face. Her skin was noticeable for its waxy pallor and was not discolored except for a small area of brownish pigment on the forehead.

The pupils of her eyes were round and equal and reacted to light. On examination of the optic fundi the disks and vessels appeared normal. As far as could be determined, the other cranial nerves were intact. The patient was edentulous. Her neck was not stiff. The thyroid gland was not palpable. Examination of her heart, lungs and abdomen revealed nothing remarkable. However, her blood pressure was 80/40, and her pulse rate was 54 per minute. Her temperature by rectum was 99.4 F., and her respiratory rate was 14 per minute.

Her breasts were small. Examination of the genitalia showed stenosis of the vaginal orifice. Palpation of the rectum and adjoining structures revealed no abnormal masses.

The patient's arms and legs were withdrawn from painful stimulation. (The right leg was shorter than the left.) There was no evidence of paralysis of the extremities, and the reflexes throughout were active and equal on the two sides. Plantar stimulation revealed bilateral extensor responses.

The hemoglobin was 13 Gm. per 100 cc., the erythrocyte count 4,010,000 and the white blood cell count 4,050 per cubic millimeter. Serologic tests of the blood gave negative reactions for syphilis. Examination of the urine revealed no evidence of albumin, sugar, blood or casts. The specific gravity was 1.025. A spinal puncture showed an initial pressure of 120 mm. of water with the patient in the lateral horizontal position. There were no cells, and the total protein was 51 mg. per 100 cc. Roentgenograms of the skull revealed a sella turcica of normal size. There was no evidence of suprasellar or other intracranial calcification.

Because of the history, the coma (temporarily relieved by glucose given intravenously) and the myxedematous appearance of the patient, a sample of blood was drawn so that the sugar content might be determined. The specimen was found to contain 41 mg. of glucose per 100 cc.

The patient was given 3,000 cc. of 10 per cent glucose solution overnight and was transferred to the University Hospitals the next morning (May 26).

Here the acute episode was diagnosed as an Addisonian crisis with associated hypoglycemia, secondary to the postpartum necrosis of the adenohypophysis. The blood sugar was found to be 52 mg. per 100 cc. The serum sodium value was 280 mg. per 100 cc., and the serum potassium, 22.8 mg. per 100 cc.

The patient was given desoxycorticosterone acetate for the first four days. This medication then was discontinued because of increasing generalized edema. In addition, both aqueous and oil-soluble adrenal cortex extracts were administered intramuscularly. Epinephrine hydrochloride was injected from time to time to help maintain the blood pressure. Both isotonic sodium chloride solution and glucose were given by continuous intravenous infusion. In spite of the intravenous administration of 15 per cent glucose solution and the oil-soluble and aqueous adrenal cortex extracts, the sugar content of the blood did not rise above 100 mg. per 100 cc. the first four days. On the fourth day, 50 mg. of cortisone was given intramuscularly, with resultant glycosuria. The patient was then maintained on a regimen of 25 mg. of cortisone a day for one week. The blood sugar value reached 200 mg. per 100 cc. on the fourth day of the cortisone administration.

The utilization of aqueous and oil-soluble adrenal cortex extracts, with the later addition of ¼ grain (32 mg.) daily doses of thyroid U. S. P. by mouth was continued during the hospital stay. After an initial period of intravenous administration of fluids, the patient was

Fig. 1.—Patient during the Addisonian crisis. Note the loss of pubic and axillary hair, the small breasts and the edematous appearance of the body.

given hourly feedings of a high carbohydrate, fat and protein formula, by stomach tube. When she was able to eat, she was given frequent meals.

The course of the patient's illness was stormy. Maintenance of the correct fluid balance and serum potassium level was difficult. On one occasion mild cardiac failure developed, and the patient was digitalized for a short period. However, she had no convulsion after the initiation of the continuous intravenous infusion of glucose.

For the first time in three weeks, the patient was neither stuporous nor semistuporous. During the latter part of her hospital stay she experienced an episode of abdominal pain, which gradually subsided. No cause for this could be found, and it was believed to be a result of the secondary adrenocortical deficiency.

Her condition slowly improved; she became more alert and she eventually was able to sit up. By her forty-eighth hospital day (July 11) she had progressed enough so that it was felt she could be discharged. She was returned home with instructions to take 1 cc. of oil-soluble adrenal cortex extract intramuscularly three times a day and ½ grain of thyroid U. S. P. by mouth once daily. She was told to continue eating six meals a day and was prescribed a high protein and moderate carbohydrate and fat diet with a high sodium chloride content.

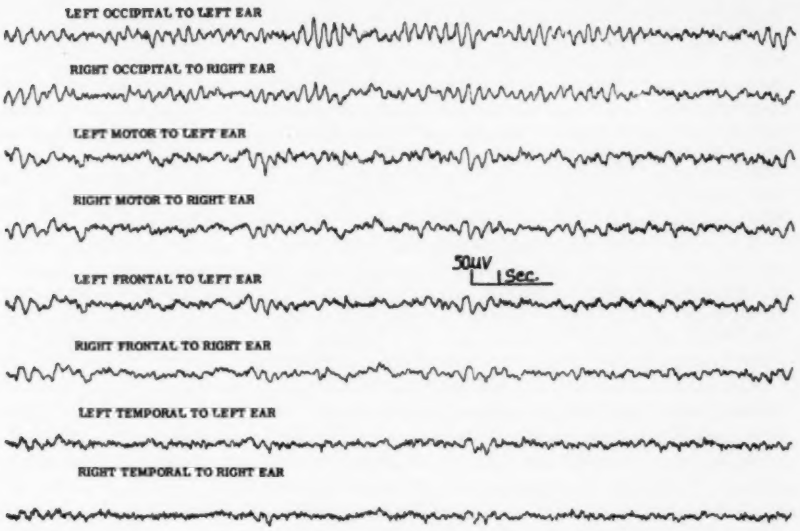

LEFT OCCIPITAL TO LEFT EAR
RIGHT OCCIPITAL TO RIGHT EAR
LEFT MOTOR TO LEFT EAR
RIGHT MOTOR TO RIGHT EAR
50uV
1 Sec.
LEFT FRONTAL TO LEFT EAR
RIGHT FRONTAL TO RIGHT EAR
LEFT TEMPORAL TO LEFT EAR
RIGHT TEMPORAL TO RIGHT EAR

Fig. 2.—Tracing showing moderate slowing of the electroencephalogram, compatible with the decreased metabolic rate.

Fig. 3.—Patient two months after discharge from the hospital. The face is less edematous.

Approximately two months later (September 20) she returned to the hospital for another examination. During the interim she had gained in strength and was able to help with the housework. She reported some increase in the hair of her eyebrows, eyelashes and scalp.

The pulse rate was 66 and the respiration rate 18 a minute. The temperature by mouth was 98.8 F. The blood pressure was 120/80. She weighed 125 pounds (56.7 Kg.) and was 60½ inches (153.7 cm.) tall. Her face and extremities had lost their puffy appearance. The congenitally dislocated right hip was again noted; in addition, weakness of the anterior tibial and peroneal muscle groups of both legs, with resultant foot drop, was found, without evidence of loss of sensation. The patient said she had first noted the bilateral foot drop at home when she started to walk. She believed some strength was returning. In view of the long time she had been bedfast and semicomatose, it was felt that the damage to the common peroneal nerves had been caused by pressure. Physical examination revealed no other significant changes.

The patient's basal metabolic rate was found to be —23 per cent. The serum sodium value was 300 mg. per 100 cc., and the serum potassium value, 17.5 mg. per 100 cc. An electroencephalogram revealed a dominant rhythm of 7½ to 8½ per second, with a scattering of faster and slower frequencies. This seemed somewhat slower than normal and was compatible with the decreased basal metabolic rate. Psychological testing with the Wechsler-Bellevue Adult Intelligence Test, Form I, revealed an average intelligence.

The results of the Wechsler Memory Scale, Form II, and the Hunt-Minnesota Test of Organic Brain Damage showed no detectable impairment in the intellectual spheres. The visual fields were full, with no defects or scotomas. A gynecological examination showed stenosis of the vagina. A sound could, however, be inserted about 3 inches (7.5 cm.). The uterus could be felt through the rectal wall and was thought to be small.

As the patient had showed marked improvement, it was felt that her medication could be decreased and desoxycorticosterone acetate added. Consequently, she was discharged, with instructions to take 0.5 cc. of oil-soluble adrenal cortex extract intramuscularly twice a day, 1.25 mg. of desoxycorticosterone acetate intramuscularly once a day and ½ grain of thyroid U. S. P. by mouth daily.

Five weeks later (October 27), during another visit, the desoxycorticosterone acetate was ordered to be discontinued because of increasing edema of the patient's face, hands and feet. At this time, the dose of thyroid was increased to ¾ grain (48 mg.) a day. The dose of oil-soluble adrenal cortex extract was not changed.

When Mrs. F. H. made her next visit, on Nov. 10, 1950, the fasting blood sugar was found to be 72 mg. per 100 cc. The basal metabolic rate was —10 per cent.

COMMENT

Trauma, fibrosis, tumor and granulomatous lesions may cause sufficient destruction of the adenohypophysis to produce pronounced hypofunction of the gland. However, according to Sheehan,[2c] the commonest cause is ischemic necrosis of the gland, secondary to postpartum hemorrhage and collapse. The following discussion will be limited to this type of lesion. Sheehan [2a,b] explains the pathogenesis of postpartum necrosis of the adenohypophysis in the following manner:

Normally, after delivery, there is a rapid involution of the pituitary gland from its physiologically hypertrophied state during pregnancy. The blood supply of the gland is suddenly diminished. If this decrease is complicated by circulatory collapse, most often due to hemorrhage, the blood flow may be reduced to an extremely low level.

Thrombosis may occur in the vascular sinuses of the gland, and consequent infarction and necrosis may be the result. This chain of events is usually precipitated by such complications as placenta previa, ruptured uterus, cervical tears, postpartum atony and retained placenta.

The typical early lesion in the anterior lobe of the pituitary is "coagulative necrosis" or "ischemic infarct," apparently secondary to the formation of fibrin thrombi in the vascular sinuses of the gland.[2b] The tissues in the posterior superior angle and a very thin layer on the surface of the gland usually escape infarction. The middle and posterior lobes of the pituitary are rarely damaged.[4] In the chronic case, with extensive infarction of the anterior lobe, the normal structure of this portion of the gland is largely replaced by connective tissue. In the severe cases the part of the gland that remains is generally less than 10 per cent of the original volume. The surviving glandular cells are usually chromophobe in type.

The thyroid gland and the adrenal cortex are usually small and atrophic in this disorder,[4] along with the changes in the adenohypophysis.

Changes in the ovaries and secondary sex organs are similar to, but are more extensive than, those occurring in senile involution. Although they are normal histologically, the heart, lungs, liver, kidneys and, to a less extent, the gastrointestinal tract may show a decrease in size.

The brain has generally been described as normal.[3] Wadsworth and McKeon [5] noted degenerative changes in the supraoptic and paraventricular nuclei of the hypothalamus, which they believed were secondary to the pathological changes in the adenohypophysis. Scattered through other areas of the brain they observed petechial hemorrhages, subependymal gliosis and degenerative cell changes, which they suggested were caused by hypoglycemia.

The frequency of this disorder is undoubtedly higher than is generally believed. Sheehan [2c] has estimated that the incidence in Great Britain is approximately two severe and seven mild cases per 10,000 of the population.

The various clinical signs and symptoms may develop at different times over a period of years. As is demonstrated in this case, when destruction of the adenohypophysis is severe, menstruation may cease, and libido is usually lost immediately after the difficult delivery. There is often disappearance of body hair, and the patient becomes apathetic and dull. A myxedematous appearance may develop, and the skin may assume a waxy pallor. In contrast to the patient with primary chronic adrenocortical insufficiency, the woman with postpartum necrosis of the anterior lobe of the pituitary may show little or no abnormal pigmentation of the skin. The teeth are gradually lost, and the breasts may decrease in size. A mild to moderate anemia is often present. At times the blood pressure is low, and the basal metabolic rate is below normal. The vagina becomes small and atrophic, and the uterus decreases in size. Finally, an Addisonian crisis may develop with hypoglycemia and, on occasion, secondary convulsions. At such times the patient is likely to become comatose and die. Women with milder types of the disorder may show various combinations of the above symptoms in less severe form.[2c]

It should be emphasized that emaciation is not frequently seen in this particular disorder. Because of a misconception that severe loss of weight is a necessary finding in extreme insufficiency of the adenohypophysis, some authors have mistakenly included instances of anorexia nervosa under the term "Simmonds' disease." [3]

4. Sheehan and Murdoch.[2b] Farquharson.[3]

5. Wadsworth, R. C., and McKeon, C.: Pathologic and Mental Alterations in a Case of Simmonds' Disease, Arch. Neurol. & Psychiat. **46**:277-296 (Aug.) 1941.

The blood sugar is invariably low in patients with postpartum necrosis of the adenohypophysis. The increased glucose tolerance in humans with this disorder has been well authenticated.[6] Glucose tolerance tests show low fasting values and a flat type of curve. With the parenteral type of test, there may be extreme depression of the blood glucose level, usually at the end of three hours. At such times, hypoglycemic shock, or an Addisonian crisis, may develop. Therefore, extreme caution must be exercised in giving an intravenous glucose tolerance test to these patients.

A number of factors may be responsible for the increased carbohydrate tolerance. Absence of activity of the anterior lobe of the pituitary would favor unopposed hexokinase and insulin activity.[7] In addition, lack of adrenocortical secretion would mean decreased 11-oxysteroid secretion and resultant decreased gluconeogenesis and increased glucose tolerance.

The correct diagnosis of extreme insufficiency of the adenohypophysis secondary to postpartum necrosis of the gland is essential for the institution of proper therapy. Women with this condition frequently are thought to have primary myxedema, chronic adrenocortical deficiency, primary gonadal insufficiency, tumors of the pancreatic islet cells and prolonged debility following a difficult labor.[8] This disorder has been mistakenly diagnosed as epilepsy, brain tumor, psychoneurosis and various types of psychosis.[9]

As demonstrated in the case reported, the treatment of the chronic form of this disease should attempt to correct the secondary glandular deficiencies through the use of cortisone, other adrenal cortex extracts and thyroid extract. The dosage of these preparations will depend on the amount of adrenal cortex and thyroid gland still functioning. Thyroid extract, however, must be used with extreme care. Unless the dose is small and simultaneous therapy for the associated adrenocortical deficiency is given, serious, and even fatal, attacks of Addisonian crisis and hypoglycemia may occur.[2d]

SUMMARY AND CONCLUSIONS

A case of extreme insufficiency of the adenohypophysis, frequently designated as "Simmonds' disease," is reported. The symptoms correspond to those described by Sheehan as following postpartum necrosis of the anterior lobe of the pituitary. The appearance of hypoglycemic convulsions was the dramatic episode which called attention to the diagnosis, although the patient had had premonitory symptoms for 17 years.

The immediate therapeutic problem revolved around the control of the Addisonian crisis and associated hypoglycemia. This end was achieved with aqueous and oil-soluble adrenal cortex extract, cortisone and parenteral injection of sodium chloride and glucose solutions. Since recovery, the patient has been adequately

6. Sheehan and Summers.[2d] Cook, J. E.; Bean, W. B.; Franklin, M., and Embick, J. F.: Postpartum Necrosis of the Anterior Pituitary Gland: Sheehan's Disease, A. M. A. Arch. Int. Med. **87**:517-532 (April) 1951.

7. Stetten, D., Jr.: Carbohydrate Metabolism, Am. J. Med. **7**:571-584 (Nov.) 1949.

8. Sheehan.[2e] Farquharson.[8]

9. Wadsworth and McKeon.[5] Frazier, C. H.: Pituitary Cachexia, Arch. Neurol. & Psychiat. **21**:1-18 (Jan.) 1929.

maintained on daily injections of oil-soluble adrenal cortex extract and the use of thyroid extract by mouth, along with frequent feedings of a high protein and moderate carbohydrate and fat diet.

In spite of a grave situation, characterized by a number of convulsions and a period of stupor lasting several weeks, the patient's intellectual functions apparently have not been impaired.

This report is intended to call the attention of the neurologist to the possibility that women who have such symptoms as amenorrhea, myxedema, adrenocortical deficiency, hypoglycemia and convulsions may have postpartum necrosis of the adenohypophysis. Emaciation is not necessarily present in this disorder. The prompt recognition of this syndrome and the immediate institution of appropriate therapy may increase the percentage of gratifying results in a condition which heretofore has offered a very poor prognosis in the severe cases.

NOTE.—During the three months since the completion of this report the patient has been receiving 20 mg. of cortisone daily by mouth, instead of the oil-soluble adrenal cortex extract. She has continued to improve and is more active now than she has been for a number of years.

EEG PROGNOSIS IN VASCULAR HEMIPLEGIA REHABILITATION

CHARLES VAN BUSKIRK, M.D.
AND
V. R. ZARLING, M.D.
MINNEAPOLIS

THE VARIOUS reports which have appeared in the literature dealing with the electroencephalogram in cerebrovascular disease and in hemiplegia have stressed the fact that a high percentage of these electroencephalograms recorded while the patient is awake are normal. Cohn, Raines, Mulder and Neumann [1] reported on 104 patients with thrombosis, embolism or hemorrhage involving the cerebral vessels. Many of these patients had electroencephalograms which returned to normal with stabilization of the clinical findings, the younger patients showing a greater tendency for this to occur. The electroencephalographic change noted was the presence of slow waves, either general or on the side of the involved hemisphere. These investigators also found that cortical damage gave rise to more slow activity than did subcortical lesions of equal size. They found that factors other than age which influenced the return of the electroencephalogram to normality were the site and the amount of cerebral damage. Cress and Gibbs [2] reported on 31 adult hemiplegic patients with chronic lesions. Of these, the hemiplegia of 24 was of vascular origin. About half the total number of patients revealed no asymmetry in the waking electroencephalogram, while 30 of the 31 patients revealed asymmetry in the sleeping electroencephalograms. Strauss and Greenstein,[3] dealing with the electroencephalogram in cerebrovascular disease, included in their report 44 patients with severe hemispheric lesions who had normal electroencephalographic recordings. These observers found that 70.5 per cent of their series of 95 patients with cerebrovascular disease had no abnormality in the electroencephalo-

From the Neurology Section, Veterans Administration Hospital and University of Minnesota Hospitals.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Cohn, R.; Raines, G. N.; Mulder, D. W., and Neumann, M. A.: Cerebral Vascular Lesions: Electroencephalographic and Neuropathologic Correlations, Arch. Neurol. & Psychiat. **60**:165-181 (Aug.) 1948.

2. Cress, C. H., and Gibbs, E. L.: Electroencephalographic Asymmetry During Sleep in Patients with Vascular and Traumatic Hemiplegia, Dis. Nerv. System **9**:327-329, 1948.

3. Strauss, H., and Greenstein, L.: The Electroencephalogram in Cerebrovascular Disease, Arch. Neurol. & Psychiat. **59**:395-403 (March) 1948.

gram. In the same series normal electroencephalograms were recorded as early as one day after the accident and abnormal records were present as long as one year after the accident. Epstein and Lennox,[4] after experimentally occluding the middle cerebral artery in dogs, were able to correlate the electroencephalographic changes in acute and chronic lesions with the resulting pathologic alterations and symptoms. These workers found that even with the lesions of greatest extent producing clinical symptoms of a lasting and severe nature, the waking electroencephalogram revealed no abnormalities eight days after the occlusion of the artery. However, sleep electroencephalograms from this group persistently revealed abnormalities. With the small lesions producing clinical symptoms of a transient nature, even the sleep records revealed no abnormality after the first week.

The present study was undertaken to determine whether there was any possible correlation between the electroencephalographic findings and the course of hemiplegia in patients on an intensive well controlled rehabilitation program.

MATERIAL AND METHODS

Electroencephalographic records of 77 patients with hemiplegia of vascular origin were obtained at varying times after the onset of the illness. In addition to the hemiplegia from which all the patients suffered, various complicating conditions were present. These included hypertension, syphilis, carcinoma, diabetes, myocardial infarction, polycythemia, phlebothrombosis, auricular fibrillation, pneumonia and myocarditis. No effort at selection was made other than that the patient have hemiplegia with a vascular origin. However, those patients who were so ill that they died of the initial accident were not included, since the object of this study was to determine the speed and degree of retraining of the patient in relation to the electroencephalographic pattern. Four patients of the group died during the period of rehabilitation—one of thrombosis of the internal jugular vein, one of a second thrombosis of an intracerebral vessel, one of coronary occlusion and one of a second intracerebral hemorrhage.

The ages of the patients ranged from 21 to 82 years, most of the patients being in the sixth decade of life. The age distribution was as follows: Four in the third decade; 4 in the fourth decade; 12 in the fifth decade; 44 in the sixth decade; 8 in the seventh decade; 4 in the eighth decade, and 1 in the ninth decade.

The time from accident to recording ranged from six days to seven years. Usually, however, recordings were made when it was believed that the patient could cooperate fully and would not suffer from the necessary manipulation. All records were made using a Grass six or eight channel electroencephalograph. Thirteen electrodes of the solder disk type, with homologous placements over the frontal, motor, parietal, occipital and temporal areas, with ear electrodes and a motor vertex electrode, were routinely used. Recordings were made from scalp and ear electrodes and from scalp to scalp electrodes in various combinations. A few recordings were also made using alternate ears, as a reference point to the homologous scalp electrodes of the hemispheres. No records were taken while the patient was receiving any of the barbiturate drugs. A few records also were taken while the patient was drowsy or sleeping, but only the waking records were considered in this study. Hyperventilation of three minutes' duration was routinely employed to provide physiological stress. Serial electroencephalograms were obtained from eight patients.

Classification of the records was made on the Gibbs system, based on frequency. Since preliminary survey indicated no conspicuous hypersynchronous changes in any record, the classification based on frequency was considered to be most useful. The S1 classification was used when the major portion of the record was in the frequencies of 4 to 7 cycles per second;

4. Epstein, J. A., and Lennox, M. A.: Electroencephalographic Study of Experimental Cerebrovascular Occlusion, Electroencephalog. & Clin. Neurophysiol. **1**:491-502, 1949.

S2, when the major portion of the record had a frequency below 4 cycles per second, and S3, when the major portion of the record had a frequency below 2 cycles per second. A further classification of amplitude asymmetry, defined as a constant difference of over 30 microvolts, was used, and this only after careful checking of symmetrical electrode placements had been made. In general, the asymmetry was hemispheric rather than between homologous electrodes.

RESULTS

Patients with normal electroencephalograms on the initial examination showed neurological dysfunction equal in degree to that found in patients with abnormal electroencephalograms; consequently, it was impossible to correlate the initial dysfunction with the electroencephalogram. There may be a — 1 degree to absence of muscle strength, aphasia, pseudobulbar symptoms, homonymous hemianopsia,

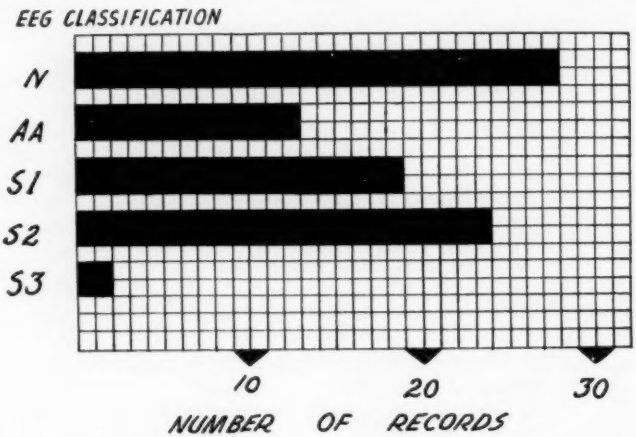


Chart 1.—Data on electroencephalographic records in hemiplegic patients classified according to frequency and amplitude asymmetry.

hemihypesthesia and decreased vibratory and stereognostic sense in patients with either normal or the S2 type of electroencephalographic pattern.

The frequency distribution of the various patterns can be seen in chart 1 for all the 86 electroencephalograms in this series. As may be noted, 32 per cent of the records were normal; 15 per cent revealed only significant amplitude asymmetry; 22 per cent were of S1 type; 27 per cent, of S2 type, and 2 per cent, of S3 type.

The age distribution reveals that the majority of the patients were in the same age range (51 to 60 years). No correlation can be made between the age of the patient in this series and the pattern of his electroencephalogram. However, age has some significance in regard to the degree of recovery, since of the 20 patients who were 50 years of age or less, all but five made a better than minimum degree of recovery.

Since in the rehabilitation program the patient is urged to make as rapid progress as possible, and since he is discharged or transferred as soon as a plateau

of performance is achieved, it is believed that the hospital stay is a fairly good index of speed of recovery. There are, of course, some few patients who do not achieve enough return of function to be eligible for a domiciliary home and so remain in the hospital. Correlation of the hospital stay of the patient and the electroencephalogram (chart 2) reveals that of 16 patients remaining in the hospital less than 30 days, 12 showed normal electroencephalograms and only 1 an S2

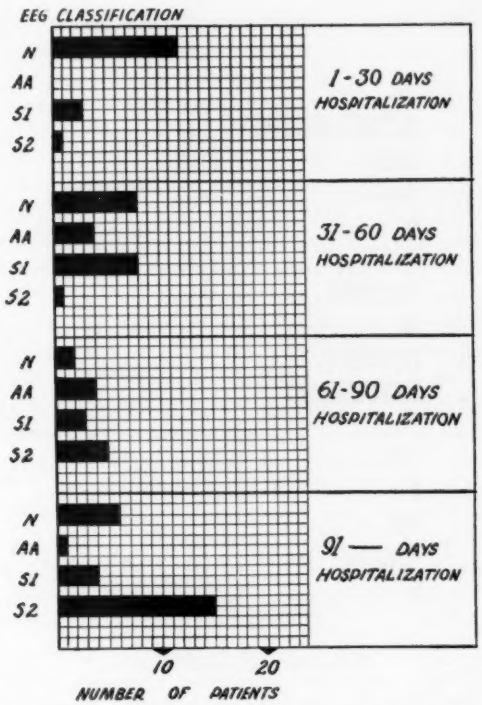


Chart 2.—Electroencephalographic classification in relation to time required for accomplishment of maximal rehabilitation.

record. Patients staying over 90 days comprised a group of 26, of whom 6 had records which were normal and 15 abnormal electroencephalograms of the S2 type.

It is the policy for the patient to remain in the hospital until he has reached either a minimum level of performance, which includes all self-care activities and useful ambulation without aid, as has previously been outlined by Leemhuis and Brown,[5] or has ceased to improve in spite of an intensive program of rehabilitation. Self-care activities include washing, shaving, dressing, toilet care and feeding.

5. Leemhuis, A. J., and Brown, J. R.: Treatment of the Hemiplegic Patient, Journal-Lancet **70**:90-93, 1950.

Ambulation includes walking, climbing stairs and crossing the street. These may be achieved though there may remain severe motor disability. Correlation of the discharge disability with the electroencephalographic record (chart 3) reveals that most of the records of the patients who were discharged with a better than minimum level of performance were normal and that in this group there was only one S2 record. In the group of patients with minimum performance there were more abnormal than normal records, but the proportions of normal, S-1 and S-2 records were close. However, the largest group of records of the group with less than minimum performance were of the S2 type, and the only S3 record in the series lay in this group.

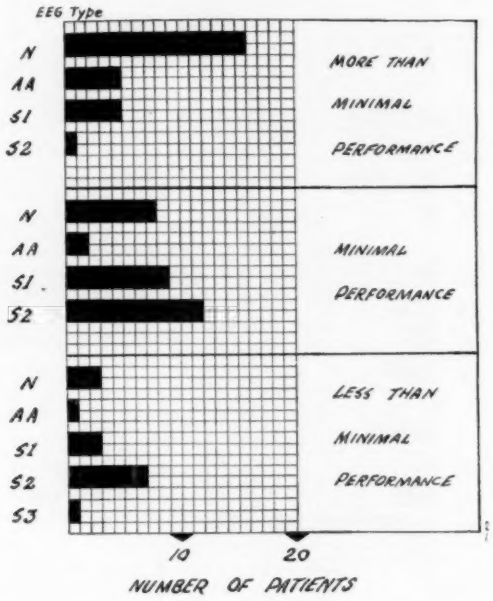


Chart 3.—Electroencephalographic classification in relation to degree of rehabilitation.

Examination of the material in regard to the time elapsing between onset of illness and time of recording reveals that the records made in the first month show a greater proportion of normal patterns than do those with a greater lapse of time following the onset of the illness. The records obtained more than 125 days after the accident show a greater proportion of the S2 type.

Examination of the data in regard to focal electroencephalographic patterns reveals that focal patterns constituted only 7.6 per cent of the records exhibiting only amplitude asymmetry, 15.7 per cent of the S1 group, 45.8 per cent of the S2 group and 100 per cent of the S3 group. In relation to the number of days from the onset of the accident until the recording was made, 22.5 per cent of all records made within the first month after onset of the illness were focal in pattern; of the

records made between 31 and 60 days after the onset, 21.4 per cent were focal. Of the records made 61 to 90 days after onset, 20 per cent were focal, and of those made more than 91 days after the onset, 25.7 per cent were focal. Of the abnormal records of all patients remaining in the hospital over 91 days, 60 per cent were focal. Only 20.6 per cent of the abnormal records of patients staying in the hospital less than 91 days were focal.

COMMENT AND CONCLUSIONS

Any speculation as to the origin of the patterns found in this series must be based on analogy, since this study is concerned only with the speed and the degree of rehabilitation. Consequently, no autopsy was performed. Further, even if autopsy were performed, any correlation of the lesions with the electroencephalogram would be open to question, since almost all the members of this series would undoubtedly exhibit widespread vascular changes. There is some evidence in the experience of other investigators that the slow waves seen are the result of damage or of dysfunction of the cortical cells. Walter and Dovey,[6] studying electroencephalographic patterns in patients with subcortical tumors, concluded that superficial tumors exhibit 1 to 3 per second activity in the region of the tumor. Deep tumors, they found, produce 6 per second activity over the site of the tumor if they still affect the cortex, but if the tumor was very deep the 6 per second activity was noted in the temporoparietal region. Cohn and associates [1] found that cortical damage in vascular disease gave rise to more slow activity, both focal and general, than did deep subcortical lesions of similar extent and volume. Zimmerman and Putnam,[7] in a study correlating histological changes of the cortical cells with the electroencephalographic abnormalities, concluded that slow waves are the result of damage to the cells of the deeper layers of the cortex. Epstein and Lennox,[4] with experimental occlusion of the middle cerebral artery in dogs, found that the cortex was spared except in the most extensive lesions. It was their observation that the more extensive lesions were those that exhibited abnormal electroencephalograms, which later returned to normal. The animals with these lesions showed lasting disability. The less extensive lesions which were deep and did not encroach on the cortex revealed no electroencephalographic abnormalities at all. It has been the experience of other investigators that deep lesions produce diffuse electroencephalographic changes and that superficial lesions exhibit focal electroencephalographic changes.

Analysis of the focal records in this series reveals that the S2 group possesses the greatest proportion of focal records. This is further support for the conclusion that the severer the electroencephalographic abnormality, the more superficial is the lesion. The converse may also be true, namely that the normal electroencephalograms found with hemiplegia are from the patients with small deep lesions. This assumption is, of course, supported by the findings of Epstein and Lennox.[4] It is doubtful whether a superficial lesion could produce hemiplegia and also result in a

6. Walter, W. G., and Dovey, V. J.: Electro-Encephalography in Cases of Sub-Cortical Tumour, J. Neurol., Neurosurg. & Psychiat. **7**:57-65, 1944.

7. Zimmerman, F. T., and Putnam, T. J.: Relation Between Electroencephalographic and Histological Changes Following Application of Graded Force to the Cortex, Arch. Neurol. & Psychiat. **57**:521-546 (May) 1947.

normal electroencephalogram, for it must of necessity be a fairly extensive lesion, or at least produce widespread dysfunction of the cortical cells. Edema resulting from a small superficial lesion could produce hemiplegia, but the electroencephalogram would be abnormal. Courville [8] found that in cases of brain tumors with edema electroencephalographic abnormalities can be recorded from the areas where the edema exists. However, the most likely site for a small lesion to produce hemiplegia would be deep, in or near the internal capsule. Such a lesion was found by Epstein and Lennox [4] to produce transient disability in the dog and a normal electroencephalogram even in sleep.

It is apparent from this series that the more abnormal the waking electroencephalogram of the surviving hemiplegic patient, the longer will be his hospital stay and the less will be his recovery of function on the rehabilitation service. The experience of others suggests that this is due to a more superficial and extensive lesion. The hemiplegic patient with a normal electroencephalogram may expect a greater degree of rehabilitation and a shorter hospital stay. The lesion in this patient is probably small and deep.

Examination of the data concerning focal abnormal electroencephalograms in relation to the hospital stay of the patient revealed that there was a greater proportion of focal electroencephalograms among those patients staying in the hospital over 91 days than in the group of patients staying a shorter time. This again suggests that in the hemiplegic patient whose lesion encroaches on the cortex the damage is more extensive and so recovery will be less complete and more prolonged.

This series reveals a greater number of normal electroencephalograms among those records made soon after the onset of the illness and a greater proportion of abnormal records among those made at a later time. This is to be expected, since it is the patient with the severest and most prolonged disability who has the most abnormal electroencephalogram. It is this patient who will have an electroencephalographic record made some time after the onset of his illness, since he is the one who will still find it necessary to remain in the hospital or to apply for admission to the hospital, even though considerable time has elapsed from the time of onset of his illness. The converse of this is also true for the patient with a normal electroencephalogram.

Study of these records indicates that the electroencephalogram may be useful in determining the prognosis for rehabilitation of the hemiplegic patient. The purpose of the rehabilitation service is at the least to render the hemiplegic patient able to care for his own personal needs and at the most to return to a gainful occupation. This study may indicate that it is the cortex which is most necessary for the patient in relearning the activities which he lost when his accident occurred. Involvement of the motor cortex or subcortical projection fibers can produce similar clinical symptoms in the presence of strikingly different electroencephalograms. However, it would appear that it is associated cortex destroyed along with the motor cortex which is important in the results of rehabilitation. For this reason, patients with abnormal electroencephalograms and apparently cortical lesions do not do as well on a rehabilitation program as those with normal electroencephalograms and apparently deeper-seated lesions.

8. Courville, C. B.: The Effect of Certain Lesions of the Brain on Electroencephalographic Wave Patterns: A Preliminary Study, Bull. Los Angeles Neurol. Soc. **14**:119-148, 1949.

SUMMARY

In a series of 77 patients with hemiplegia of vascular origin, 86 electroencephalographic records were obtained, studied and correlated with the duration of time required for maximal rehabilitation. The following observations were made and conclusions reached:

Thirty-two per cent of the records were normal, and patients with such records showed a greater and speedier return of function.

The severer the abnormality of the electroencephalographic record, the longer was the hospital stay and the severer the residual disability.

No correlation could be made between the degree of neurological disability at the onset of the illness and the degree of electroencephalographic abnormality.

The electroencephalogram can be a useful tool in determining the prognosis for the ease and degree of rehabilitation in a patient with vascular hemiplegia.

EFFECT OF ELECTROSHOCK ON THE BLOOD PRESSURE IN PSYCHOTIC PATIENTS

WALTER W. IGERSHEIMER, M.D.
AND
JAMES A. F. STEVENSON, M.D.
NEW HAVEN, CONN.

REMARKABLY few studies of the effect of electroshock on the blood pressure in animals or humans have appeared in the literature of recent years, although this subject found considerable attention in the early decades of this century.[1] With the invention of the modern electroshock apparatus [2] this problem was

Prof. George S. Mahl gave assistance in the analysis of the results presented in this paper.

From the Department of Psychiatry, Yale University Medical School, and the Connecticut State Hospital, Middletown, Conn.

This work was carried out under tenure of a James Hudson Brown Memorial Research Fellowship held by Dr. Igersheimer.

1. (*a*) Prévost, J. L., cited by Bini, L., and Puddi, V.: Ricerche sperimentali sulla fisiopatologia degli apparati cardiovasculari e respiratori nell 'elettroshock, Riv. sper. di freniat. **64**:563, 1940. (*b*) Battelli, F.: La mort et les accidents par les courants électriques industriels, Rev. méd. de la Suisse Rom. **22**:637, 1902. (*c*) Tatum, cited by Battelli.[1b] (*d*) Oliver, cited by Battelli.[1b] (*e*) Bolan, cited by Battelli.[1b] (*f*) Prévost, J. L., and Battelli, F.: L'épilepsie expérimentale, Encéphale **2**:165, 1907; (*g*) Expériences relatives à l'épilepsie expérimentale, Rev. neurol. **16**:850 and 914, 1907; (*h*) Quelques efféts des décharges électriques sur le coeur des mammifères, J. de physiol. et de path. gén., 1900; (*i*) Production d'accès épileptiformes par les courants électriques industriels, Compt. rend. Soc. biol. **55**:903, 1903. (*j*) Zimmern, A., and Dimier, G.: Sur la production du coma épileptique par l'excitation cérébrale au moyen des courants de Leduc, ibid. **55**:883, 1903. (*k*) Leduc, S.: Production du sommeil et de l'anesthésie générale et locale par les courants intermittents de basse tension, Compt. rend. 2e Cong. internat. d'électrol. et de radiol. méd., 1902. (*l*) Leduc, S.; Rousseau, A., and Malherbe: Production de l'inhibition cérébrale chez l'homme par les courants électriques, Compt. rend. Soc. biol. **54**:1297, 1902. (*m*) Robinovitch, L. G.: Sommeil électrique, inhibition des mouvements volontaires et de la sensibilité, par courants électriques de basse tension et à interruptions, modérément fréquentes: Épilepsie électrique et électrocution, Thesis, Paris, No. 410, Nantes, Dugas et Cie, 1906. (*n*) Gouin: Étude de l'épilepsie expérimentale par les courant intermittent de basse tension, Thèsis, Bordeaux, 1904. (*o*) Roos, S., and Koopermans, S.: Studi sulla cosidetta narcosi electrica degli animali, Vet. J. **90**:232, 1934. (*p*) Koch, H., and Sack, G.: Elektronarkoseversuche: Untersuchungen über die Wirkung periodischer rechtwinkliger Gleichstromstösse, Ztschr. f. d. ges. exper. Med. **90**:365, 1933. (*q*) Koeppen, S.: Bemerkungen zu elektrischen Unfällen, München. med. Wchnsch. **81**:974, 1934; (*r*) Der elektrische Tod, Elektrotechnische Ztschr. **34**:855, 1934; (*s*) Systematische Untersuchungen über die Wirkung des elektrischen Stromes auf den Blutkreislauf, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1935, p. 252.

2. Cerletti, U., and Bini, L.: L'elettroshock, Arch. gen. di neurol., psichiat. e psicoanal. **19**:266, 1938.

reinvestigated. Bini [3] and Delay,[4] using dogs, found that for 10 to 15 seconds immediately following an electroconvulsion the systolic blood pressure oscillated or fell slightly, while the diastolic blood pressure either remained unchanged or fell. With the beginning of a grand mal seizure the systolic blood pressure quickly rose to markedly hypertensive levels, while the diastolic blood pressure remained relatively unchanged. The systolic hypertension persisted for 60 to 180 seconds, even after complete cessation of the convulsions. The systolic and diastolic blood pressures then dropped gradually to below pretreatment values, remaining at hypotensive levels from several hours to three days. Vagal section increased the duration of the hypertensive phase. Asphyxia produced a sudden fall of blood pressure, but maintenance of artificial respiration with a mixture of carbon dioxide and oxygen permitted the usual systolic hypertension, which was, however, considerably prolonged. The repetition of as many as 31 electroconvulsions did not modify the blood pressure responses appreciably.[3] These changes were attributed to stimulation of the vagal nuclei [3] or the diencephalic centers controlling the equilibrium between the sympathetic and the parasympathetic system.[4] Accornero,[5] and later Deshaies and Renault,[6] noted that on administration of electroshocks to psychotic patients there occurred a definite systolic and a slight diastolic hypertension, lasting about five minutes and followed by systolic and diastolic hypotension, which persisted from one hour to three days. Comparing the mean resting blood pressure levels in the pretreatment, treatment and post-treatment phases, Deshaies and Renault observed that after the first few treatments there existed in most patients a downward trend of both the systolic and the diastolic blood pressure. Toward the end of the treatment phase, the mean blood pressures assumed a variety of patterns and ranged from hypotensive to hypertensive levels. In the post-treatment phase the mean blood pressure tended to return to the pretreatment level. The authors attributed these changes to electrical stimulation of neurovegetative centers in the diencephalon and to the added effect of a severe shock on the total organism. Control data on a similar group of patients not receiving electroshock therapy, to rule out the possible effect of simple rest in a hospital environment, were, however, not obtained. Funkenstein [7] noted a decrease in the basal blood pressure after electroshock therapy and stated the belief that this was due to a lowering of the basal sympathetic tension, particularly when this had been increased by illness. Moore,[8] on the basis of experience with extensive clinical series, did not consider hypertension a contraindication to electroshock therapy. Furthermore, a number of investigators stated that patients with a systolic hypertension of 200 mm. of mercury

3. Bini, L., and Puddi, V.: Ricerche sperimentali sulla fisiopatologia degli apparati cardiovasculari e respiratori nell 'electroshock, Riv. sper. di freniat. **64**:653, 1940.

4. Delay, J.: L'electro-choc et la psycho-physiologie, Paris, Masson & Cie, 1946.

5. Accornero, F.: Comportamento del polso, del respiro, della pressione arteriosa, e della temperatura durante l'elettroshock, Riv. sper. di freniat. **64**:459, 1940.

6. Deshaies, G., and Renault, M.: La tension artérielle des électro-choqués, Ann. méd.-psychol. **106**:137, 1948.

7. Funkenstein, D. H.; Greenblatt, M., and Solomon, H. C.: Autonomic Nervous System Changes Following Electric Shock Treatment, J. Nerv. & Ment. Dis. **108**:409, 1948.

8. Moore, M. T.: Electrocerebral Shock Therapy: A Reconsideration of Former Contraindications, Arch. Neurol. & Psychiat. **57**:693 (June) 1947.

had not been harmed by this therapy, but that their hypertension had, in fact, sometimes been temporarily relieved.[9]

The aim of this investigation was to study, in psychotic patients, the effect of electroshock on (1) the blood pressure immediately following electroconvulsions (immediate effect); (2) the mean daily basal blood pressure (delayed effect), and (3) the reactivity of the blood pressure in response to a standard stimulus (response to the cold pressor test) before and after a series of electroshocks.

Control data bearing on delayed effects in a group of patients with mixed psychoses not receiving electroconvulsion treatments were obtained. These, as well as the investigation into the reactivity of the blood pressure, seemed to be necessary additions to a study of blood pressures undertaken previously by Deshaies and Renault.[6]

CASE MATERIAL

Immediate Effects.—A total of eight psychotic patients were studied (table 1), three of whom had involutional melancholia (cases 15, 16 and 17), two manic-depressive psychosis, depressed phase (cases 10 and 11) and three schizophrenia (cases 1, 2 and 9).

Delayed Effects.—A total of eight normotensive psychotic patients were studied (table 1), two of whom had involutional melancholia (cases 15 and 16), two manic-depressive psychosis, depressed phase (cases 10 and 11), two psychotic depressions (cases 21 and 22) and two schizophrenia (cases 1 and 2). In addition, a group of five psychotic patients with hypertension were included (cases 3, 14, 18, 19 and 20). The eight normotensive patients were compared with a control group of eight normotensive patients with mixed psychoses who did not receive electroshock treatments. Such a comparison corrects for effects on their blood pressures produced by the environment of a psychiatric hospital.

Reactivity of the Blood Pressure.—A total of 11 normotensive psychotic patients were studied (table 1), of whom four had manic-depressive psychosis (cases 10, 11, 12 and 13) and seven schizophrenia (cases 1, 2, 4, 5, 6, 7 and 8).

METHOD

Immediate Effects.—Blood pressure readings were obtained with a sphygmomanometer every five minutes for 15 minutes, the patient resting in a horizontal position. The patient was then prepared for the electroshock within 60 seconds. The shock, produced by a current varying from 200 to 250 volts, was administered 0.2 to 0.25 second and produced a grand mal seizure. No blood pressure readings were taken during the latent, tonic and clonic phases because of mechanical difficulties. Measurements usually were started two minutes after the administration of the shock and were then determined every minute during the first 10 minutes after shock, then 15, 20 and 30 minutes after shock and, when possible, 60 minutes after shock. Each patient was observed during two to five electroconvulsions.

Delayed Effects.—The blood pressure determinations in the experimental and control groups were obtained daily throughout hospitalization at basal conditions, i. e., soon after the patient wakened, while resting horizontally, and before breakfast. It was found that blood pressure levels obtained in this manner were the least variable. Simultaneous judgments of the patient's emotional status were made, and readings obtained while the patient was under obvious emotional stress were eliminated.

---

9. Evans, V. L.: Electroconvulsive Shock Therapy and Cardiovascular Disease, Ann. Int. Med. **22**:692, 1945. Kennedy, F., and Wiesel, B.: A Report on the Results of Electric Shock Treatment on Mental and Emotional Symptoms, New York J. Med. **42**:1663, 1942. Kalinowsky, L. B., and Hoch, P. H.: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune & Stratton, Inc., 1946, p. 125. Foster-Kennedy, in discussion on Moore.[8] Donnadieu, A.; Relier, and Felix, R.: Troubles mentaux et hypertension artérielle, splanchnicectomie et électro-choc (Suite d'une première observation), Ann. méd.-psychol. **104**:88, 1946.

TABLE 1.—*Index to Case Material*

Case No.	Diagnosis	Age	Sex	Duration of Illness	No. of Electro-convulsive Treatments	Symptomatic Improvement			
						Recovery	Marked	Moderate	None
1	Schizophrenia, paranoid type	22	F	6 mo.	15	..	+	..	..
2	Schizophrenia, paranoid type	39	M	2 mo.	15	+	..	..	..
3	Schizophrenia, paranoid-catatonic type	45	F	2 yr.	5	..	..	+	..
4	Schizophrenia, paranoid type	44	M	9 mo.	15	..	..	+	..
5	Schizophrenia, paranoid type	34	M	2 wk.	15	..	..	+	..
6	Schizophrenia, catatonic type	59	F	2 days	15	..	+	..	..
7	Schizophrenia, simple type	20	M	1 mo.	20	..	..	..	+
8	Schizophrenia, paranoid type	50	F	8 yr.	20	..	+	..	..
9	Schizophrenia, unclassified	42	F	2 mo.	6	..	+	..	..
10	Manic-depressive psychosis, depressed	50	M	2 wk.	12	+	..	..	..
11	Manic-depressive psychosis, depressed	43	F	4 mo.	8	..	+	..	..
12	Manic-depressive psychosis, manic	32	F	1 mo.	20	..	+	..	..
13	Manic-depressive psychosis, depressed	26	F	3 wk.	20	..	..	+	..
14	Manic-depressive psychosis, depressed	52	F	4 mo.	12	..	..	+	..
15	Involutional melancholia	44	F	2 mo.	16	..	+	..	..
16	Involutional melancholia	51	M	2 mo.	12	..	+	..	..
17	Involutional melancholia	56	F	4 mo.	15	..	..	+	..
18	Involutional melancholia	69	F	5 mo.	9	+	..	..	..
19	Manic-depressive psychosis, depressed	57	F	3 mo.	11	+	..	..	..
20	Psychotic depression	50	F	4 mo.	8	..	..	+	..
21	Psychotic depression	53	M	6 mo.	6	..	..	+	..
22	Psychotic depression	60	F	2 yr.	8	..	..	+	..

Summary

Total No. Cases									
6	Schizophrenia, paranoid type	Range	20-69 yr.	Females	15	Range	2 days-8 yr.	18.2%	36.4%	40.9%	4.5%
1	Schizophrenia, catatonic type	Mean	45.4 yr.	Males	7	Median	3 mo.				
1	Schizophrenia, simple type	Median	47.5 yr.			Mean	12.9				
1	Schizophrenia, unclassified					Median	13.5				
5	Manic-depressive psychosis, depressed										
1	Manic-depressive psychosis, manic										
3	Psychotic depression										
4	Involutional melancholia										

Reactivity of the Blood Pressure.—The cold immersion test of Hines and Brown [10] was used because it employs a standard stimulus. It is easily administered and has been found by various observers [11] to have a definite pressor effect on the blood pressure in nonpsychiatric patients. It was carried out as described by Hines and Brown, with the patient resting horizontally with one arm immersed up to the wrist in water at a temperature of 4 C. for one minute. Resting blood pressure readings were taken before the application of the cold stimulus until a stable plateau was established (for at least 30 minutes). The criterion of stability was that four successive systolic and diastolic readings should not vary more than 2 mm. of mercury above or below the mean of these four readings. For 10 minutes before and after application of the cold stimulus readings were taken every minute, while during the test observations were made 30 and 60 seconds after its inception. Movements of the patient, particularly of the head, and sources of noise were excluded as far as possible. Two such tests were performed 15 minutes apart before the administration of amobarbital (amytal®) sodium.

Since the cold pressor test is emotionally stressful and might lead to the liberation of epinephrine, muscle contractions and breath holding, an anesthesia-inducing 5 per cent solution of amobarbital sodium containing from 0.5 to 1.0 Gm., depending on the size of the patient, was then injected intravenously within three to five minutes, so that no sensation or motor response could be elicited during the test. Although amobarbital sodium may reduce the cold pressor response by 60 to 100 per cent,[10] this action seems to be proportional to the amount of the drug administered and to the time of its action (observations to be published). General anesthesia was, therefore, rapidly induced with the least amount of amobarbital sodium required to eliminate sensation and motor response and, at the same time, to avoid the ever increasing effect of the drug. Accordingly, two cold pressor tests were performed at 5 to 10 minute intervals as soon as a steady blood pressure plateau was obtained after the injection of amobarbital sodium, the criterion of stability being that stated above, but not later than 10 to 15 minutes after the inception of anesthesia.

Cold pressor tests before the induction of and during anesthesia were performed in this sequence on each patient, once before the start and once after the completion of an electroshock series.

RESULTS

Immediate Effects.—The mean over-all systolic and diastolic blood pressure responses of the eight normotensive psychotic patients subjected to electroshocks are plotted in chart 1. The mean blood pressures and standard deviations for this patient group before and at certain intervals after convulsions are tabulated in table 2.

---

10. Hines, E. A., Jr., and Brown, G. E.: A Standard Stimulus for Measuring Vasomotor Reactions: Its Application in the Study of Hypertension, Proc. Staff Meet., Mayo Clin. **7**:332, 1932.

11. Hines, E. A., Jr., and Brown, G. E.: A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State, Ann. Int. Med. **7**:209, 1933; The Cold Pressor Test for Measuring the Reactibility of Blood Pressure: Data Concerning 571 Normal and Hypertensive Subjects, Am. Heart. J. **11**:1, 1936. Hines, E. A., Jr.: Reaction of the Blood Pressure of 400 School Children to a Standard Stimulus, J. A. M. A. **108**:1249 (April 10) 1937; Technic of the Cold Pressor Test, Proc. Staff Meet., Mayo Clin. **14**:185, 1939; The Significance of Vascular Hyperreaction as Measured by the Cold-Pressor Test, Am. Heart J. **19**:408, 1940. Yates, M. R., and Wood, J. E., Jr.: Vasomotor Response of Non-Hypertensive Individuals to a Standard Cold Stimulus, Proc. Soc. Exper. Biol. & Med. **34**:560, 1936. Ayman, D., and Goldshine, A. D.: Cold as a Standard Stimulus of Blood Pressure: Study of Normal and Hypertensive Subjects, New England J. Med. **17**:650, 1938. Miller, J. H., and Bruger, M.: The Cold Pressor Reaction in Normal Subjects and in Patients with Primary (Essential) and Secondary (Renal) Hypertension, Am. Heart J. **18**:329, 1939. Feldt, R. H., and Wenstrand, D. E. W.: The Cold-Pressor Test in Subjects with Normal Blood Pressures: Report of Observations on 350 Subjects with Special Reference to Family History, ibid. **23**:766, 1942. Russek, H. I.: The Significance of Vascular Hyperreaction as Measured by the Cold Pressor Test: Observation on 200 Normal Subjects over Age of 40, ibid. **26**:398, 1943.

The significance of the differences between these means was determined by the *t*-test for related measures. The results of the *t*-test, expressed as *p* values, are shown in table 3. The systolic blood pressures rose significantly and rapidly to a peak two to three minutes after shock, fell progressively and significantly between two to three and six to seven minutes after shock but was still significantly higher 10 minutes after shock than the preshock level. It returned to levels not significantly different from preshock values within 20 minutes after shock. The mean diastolic blood pressures of the entire group following electroconvulsions did not differ significantly from the preshock levels, although individual postshock diastolic blood pressure levels were moderately labile up to 10 minutes after treatments.

It seemed of interest to mention the atypical blood pressure responses to electroshock treatment of a white woman aged 53 with essential hypertension whose psychiatric diagnosis was manic-depressive psychosis, depressed phase [19-8] (chart 1).

TABLE 2.—*Summary of Immediate Effects of Electroshock on Blood Pressure*

Time of Measurement	Mean Blood Pressure (n = 8)		Standard Deviation	
	Systolic	Diastolic	Systolic	Diastolic
	Pretreatment			
During 15 min. of rest	115	72	11.65	5.21
	Post-Treatment			
2-3 min.	159	68	13.05	13.69
6-7 min.	128	63	18.6	12.43
10 min.	122	70	11.01	4.39
20 min.	119	74	13.65	8.34
30 min.	117	78	3.12	8.04

TABLE 3.—*Significance of Changes in Mean Blood Pressures on Comparison of Measurements at Various Time Periods Before and After Electroshock*

Time Measurements Compared at:	*p* Value	
	Systolic	Diastolic
0* vs. 2-3 min	<0.001	<0.30
2-3 min. vs. 6-7 min	<0.001	<0.40
0 vs. 10 min	<0.06	No significant difference by inspection
0 vs. 20 min	No significant difference by inspection	

* 0 is resting preshock phase.

The mean blood pressures during two observation periods revealed a sharp postshock drop of both the systolic and the diastolic blood pressure. Thereafter, both pressures rose somewhat, remaining, however, lower than preshock levels for 30 minutes.

Delayed Effects.—The daily basal blood pressures were obtained for five time intervals of about 10 days each, corresponding to a preshock phase, three shock phases, during each of which three to five electroshock treatments were given, and a postshock phase. The mean over-all basal systolic and diastolic blood pressures for eight normotensive psychotic patients were calculated for each time period and are plotted in chart 2. They are compared in this graph with those for eight nonhypertensive patients with mixed psychoses from the same ward environment who did not receive electroshock treatments, but whose basal blood pressures were obtained and averaged for similar time periods (chart 2).

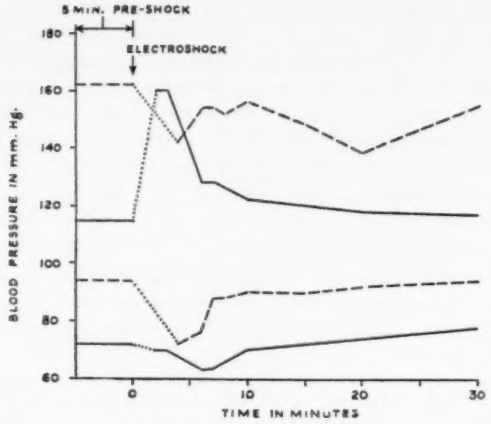


Chart 1.—Immediate effect of electroshock on the blood pressure in psychotic patients. The solid line indicates mean blood pressure changes of eight normotensive psychotic patients; the line of dashes, mean blood pressure changes of a hypertensive psychotic patient; the line of dots, the time interval during which no measurements were obtainable.

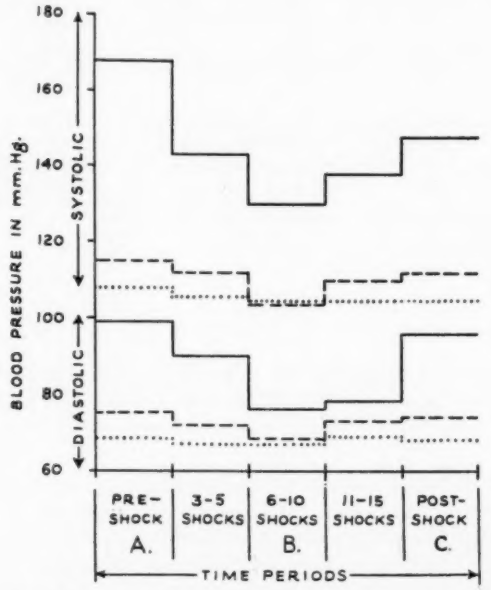


Chart 2.—Delayed effect of electroshocks on the basal blood pressure in psychotic patients. The solid line indicates mean basal blood pressures of the hypertensive group; the line of dashes, mean basal blood pressures of the experimental group; the line of dots, mean basal blood pressures of the control group.

Basal blood pressure readings were taken by the same 11 nurses in both the experimental and the control groups. Four additional nurses took measurements in the experimental group. Of these, one nurse took a significant number of readings, while the other three nurses made an insignificant number of determinations. The following methods were used to obtain an estimate of the variability in blood pressure measurements which could be attributed to the variability in reliability of the nurses making the measurements:

1. Spot checks by the investigator were made at frequent intervals and were found to correspond closely to the nurses' observations.

2. The three most significant phases of blood pressure determinations, namely, the preshock phase, the six to 10 shock phase and the postshock phase, were selected.

TABLE 4.—*Delayed Effects of Electroshock on Basal Blood Pressures*

Time Phase *	Mean Blood Pressure (n = 8)		Standard Deviation	
	Systolic	Diastolic	Systolic	Diastolic
	Experimental Group			
A	115	75	10.14	7.92
B	104	68	7.46	4.59
C	112	74	15.65	8.25
	Control Group			
a	108	68	7.52	5.13
b	105	68	6.74	6.89
c	105	68	7.85	8.16

* In this table, and in tables 5 and 6, A, B and C refer to the preshock (A), 6-10 shock (B) and postshock (C) phases for the experimental group; a, b and c refer to time intervals for the control group comparable to those for the experimental group.

TABLE 5.—*Delayed Effects of Electroshock on Basal Blood Pressures**

Time Phases * Compared	p Value	
	Systolic	Diastolic
Experimental Group		
A vs. B	<0.01	<0.01
B vs. C	<0.09	<0.10
A vs. C	No significant difference by inspection	
Control Group		
a vs. b	<0.15	No significant difference
b vs. c	No significant difference by inspection	
a vs. c	<0.20	No significant difference

* Significance of differences within each group between different time intervals as determined by the t test for related measures.

Comparisons of the median blood pressures, as obtained by the nurses, were made in each phase if at least two nurses had taken at least three readings in a phase. Of 12 nurses, the readings of 10 could be compared for similar periods, and no striking difference was found between the medians of their measurements.

3. Rough inspection revealed no gross differences in reliability among the nurses.

It would have been preferable to have the same nurses make all the basal blood pressure measurements and to know the reliability of these measurements; but on the basis of the findings just noted, it is concluded that no sizable error was introduced into the results by the factor of variability in the nurses. Consequently, it is felt that any significant changes in these basal values cannot be attributed to this factor.

The basal blood pressure measurements of the experimental and the control groups were analyzed in two ways:

First, the significance of the changes within each of the two groups was tested by the *t*-test for related measures. The results of this analysis are shown in tables 4 and 5. In the experimental group a significant drop in systolic and diastolic blood pressures was found when the mean blood pressures in the preshock phase were compared with those for the six to 10 shock phase. On completion of the series of electroshocks, the experimental group showed a fairly significant rise of systolic and diastolic blood pressures, so that no significant difference could be found between the systolic and diastolic mean blood pressures obtained before and those obtained after shock. The control group did not show any significant changes in blood pressure when the systolic and diastolic means for similar time intervals were compared.

Second, the basal blood pressure changes of the experimental group were compared with the changes of the control group; i. e., the net differences between the two groups were analyzed. F tests were used to determine the significance of differences in the variability of these changes. There was no significant difference between the two groups in the variability of the change from the pretreatment phase

TABLE 6.—*Delayed Effects of Electroshock on Blood Pressure**

Time Phases Compared	p Values			
	Differences in Variability: *F*-Test		Differences Between Means: *T*-Test	
	Systolic	Diastolic	Systolic	Diastolic
A-B vs. a-b.....	No significant difference		<0.01	<0.04
B-C vs. b-c.....	<0.01	<0.01	<0.08	<0.11

* Comparison of differences in basal blood pressure changes between various phases of electroshock therapy in the experimental group, as compared with basal blood pressure changes in the control group during similar time intervals as determined by the *t* test for independent samples.

Where *F* was significant (i. e., $p < 0.05$) the p value for the *t* test was adjusted for its difference in variability between the samples according to the method described by Snedecor (Snedecor, G. W.: Statistical Method, Applied to Experiments in Agriculture and Biology, ed. 4., Ames, Iowa, The Collegiate Press, Inc., 1946).

to the six to 10 shock phase. The changes in both systolic and diastolic pressures from the six to 10 shock to the postshock phase of the experimental groups were significantly more variable than the corresponding changes of the control group. While the actual numerical data of these changes are not presented, the p values are entered in table 6.

The mean decreases in the systolic and diastolic blood pressures from the preshock to the six to 10 shock phase of the experimental group were significantly more variable than the corresponding changes of the control group (table 6). The mean increases in the systolic and diastolic blood pressures from the six to 10 shock to the postshock phase of the experimental group showed a tendency to be significantly greater than the corresponding changes of the control group. The latter comparisons include an adjustment for the significant differences in variability noted above (note, table 6).

Hypertensive Group: Five hypertensive patients with mixed psychoses who received a course of electroshock treatments were observed in similar manner. Their mean systolic and diastolic blood pressures in the various phases of treatment are plotted in chart 2. Comparison with a hypertensive psychotic control group not

receiving electroshocks is planned, but has not yet been carried out. At present it is noteworthy that marked systolic and diastolic hypotension became maximal in the six to 10 shock phase. Thereafter, both blood pressures tended to rise gradually but remained at a hypotensive level sometimes for four to eight weeks after shock.

Effects on Reactivity of the Blood Pressure.—Seven normotensive patients with schizophrenia and four normotensive patients with manic-depressive psychoses submitted to cold pressor tests before and after the administration of amobarbital

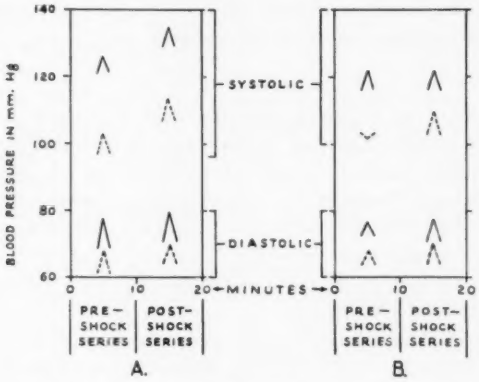


Chart 3.—Reactivity of the blood pressure in psychotic patients measured before and after electroshock series.

A, shows values for 7 normotensive patients with schizophrenia; *B*, 4 normotensive patients with manic-depressive psychosis.

The solid line indicates mean cold pressor responses before amobarbital sodium was administered; the line of dashes, mean cold pressor responses while the patient was under the effect of amobarbital sodium.

TABLE 7.—*Reactivity of Blood Pressure in Psychotic Patients in Response to the Cold Pressor Test*

Diagnosis	Experimental Condition	Before Electroshock				After Electroshock			
		Mean Blood Pressure		Standard Deviation		Mean Blood Pressure		Standard Deviation	
		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Normotensive schizophrenic patients (7)	Resting blood pressure	120.4	69.0	10.6	6.22	129.0	71.0	7.1	10.39
	Cold pressor test	+6.3	+9.3	3.68	6.47	+5.9	+8.7	5.46	2.69
	Resting blood pressure under amobarbital sodium	97.6	60.7	12.39	7.52	107.0	64.4	6.22	3.58
	Cold pressor test under amobarbital sodium	+5.7	+6.9	3.11	2.97	+4.86	+6.71	5.55	2.98
Normotensive manic-depressive patients (4)	Resting blood pressure	116.8	73.0	9.81	14.45	116.8	71.0	3.86	6.83
	Cold pressor test	+5.8	+4.5	4.99	1.73	+5.8	+7.8	5.50	4.35
	Resting blood pressure under amobarbital sodium	102.5	64.3	6.03	12.42	102.8	64.0	1.50	6.73
	Cold pressor test under amobarbital sodium	−0.5	+4.5	3.11	1.73	+7.5	+7.5	7.72	3.42

sodium in the preshock and the postshock phase (chart 3). The means and standard deviations of the results are compiled in table 7. No significant differences were noted when the responses to preshock cold pressor tests before and under the influence of amobarbital sodium were compared with the responses to postshock cold pressor tests under similar conditions. One exception occurred in the group with manic-depressive psychoses, in which a slightly negative response to the preshock systolic cold pressor test under the action of amobarbital sodium changed to a positive response to the postshock cold pressor test. This could be explained by a stronger and faster-acting depressant effect of amobarbital sodium on the preshock systolic blood pressure in this patient group.

COMMENT

Immediate Effects.—The data confirm the work of Accornero [5] and Deshaies and Renault [6] on humans and that of Bini and Puddi [3] and Delay [4] on dogs. Although the number of patients in each disease group was too small for statistical intergroup comparison, it seemed that the over-all immediate blood pressure responses to electroshock were similar in patients with schizophrenia, manic-depressive psychosis and involutional depression. The atypical blood pressure response in one hypertensive psychotic patient found on two separate occasions warrants investigation of a larger group of such patients.

Delayed Effects.—The data are in general agreement with the results obtained by Deshaies and Renault.[6] The descending and ascending changes in systolic and diastolic blood pressures observed during a series of electroshocks may represent, respectively, the following changes in vasomotor tonus:

1. A gradually progressive loss of vasomotor tonus, which is, however, never complete. During the phase of the greatest lowering of systolic and diastolic blood pressures, an intravenous injection of tetraethylammonium chloride produced a further significant fall in both blood pressures, showing that the autonomic ganglia were permitting vasomotor-maintaining impulses to travel across them before the injection of the drug.

2. A gradually progressive recovery of vasomotor tonus.

These changes might be regarded as phenomena of partial exhaustion and adaptation of the vasomotor system in response to stress. This hypothesis is, however, entertained only with the greatest reservation, since the physiological factors, whether neural or humoral or both, producing these blood pressure changes in response to electroshock are not yet fully understood.

Effects on Reactivity of the Blood Pressure.—The results indicate that although the large majority of the patients receiving electroshock treatment recovered or showed striking or moderate clinical improvement (table 1), this was not reflected in any significant change in the cold pressor response.

During the course of this investigation it was noticed that the cold pressor responses in the patients with schizophrenia and manic-depressive psychoses were notably lower than cold pressor responses of normal subjects reported in large series. This observation will serve as the basis of a future communication.

SUMMARY

1. Immediately following the administration of electroshock to psychotic patients, there are sharp systolic hypertension and diastolic lability. Both the systolic and the diastolic blood pressure return to preshock levels within 10 to 20 minutes. Patients with different psychoses seem to have similar blood pressure responses.

The atypical blood pressure responses of a hypertensive psychotic patient are described.

2. The delayed effects on blood pressure produced by the administration of electroshock in normotensive psychotic patients are as follows:

(*a*) Systolic and diastolic hypotension is present after six to 10 electroshocks have been given.

(*b*) Thereafter both systolic and diastolic blood pressures tend to return to the preshock levels and may not reach them until two weeks after the administration of the last electroshock. This phase is characterized by a widely divergent range of basal blood pressures.

Similar, but more pronounced, effects have been found in five hypertensive psychotic patients.

3. Changes in vascular reactivity in response to the cold pressor test attributable to electroshock treatments have not been observed in psychotic patients.

ANTICONVULSANT DRUG THERAPY OF BEHAVIOR PROBLEM CHILDREN WITH ABNORMAL ELECTROENCEPHALOGRAMS

BENJAMIN PASAMANICK, M.D.
ANN ARBOR, MICH.

THROUGHOUT the history of child psychiatry a large number of physical measures have been used in an effort to influence pathological behavior in children. Electricity; surgical procedures on various bodily organs; restraints; whippings; applications of extremes of temperature; use of water internally and externally; use of fever-producing mediums; deprivation and prescription of divers foodstuffs in quality and quantity; every type of sedative and narcotic to be found in the materia medica, and administration of cathartics, allergens and antiallergens, and a host of other drugs of animal, vegetable and mineral origin, including hormones, make up only a partial list of such therapeutic attempts. Almost universally, each has been reported at one time or another to be efficacious. Almost as universally, the studies have been not well controlled, and in time many of these measures have fallen into desuetude.

In 1937 Bradley,[1] in a well controlled study, reported on the use of amphetamine (benzedrine®) sulfate in the management of childhood behavior problems. The finding of excellent results in approximately half the children has been confirmed by many other reporters, and the drug has remained one of the most useful in the armamentarium of the pediatric psychiatrist. With the pioneer electroencephalographic investigation of epileptic and problem children and the finding of numerous similarities between the two, along with a large percentage of abnormalities in the latter group, it was but a logical step to administer drugs useful in epilepsy to the problem children. Again, in 1942, the workers at the Emma Pendleton Bradley Home [2] were the first to report on the use of the new drug diphenylhydantoin (dilantin®) in their patients. They gave 300 mg. of diphenylhydantoin sodium U.S.P. daily for one week to 13 children and noted mild improvement, which was not as great as that following use of amphetamine. However, they had begun administration of the drug immediately on cessation of a week's trial of phenobarbital, which had been found to make behavior worse. In addition, they reported from the statistical point of view that the behavior of the children while receiving diphenylhydantoin was not significantly different from the behavior during the final (control) period.

From the Neuropsychiatric Institute, University of Michigan Medical School.

1. Bradley, C.: Behavior of Children Receiving Benzedrine, Am. J. Psychiat. **94**:577-585, 1937.

2. Lindsley, D. B., and Henry, C. E.: The Effect of Drugs on Behavior and the Electro-Encephalograms of Children with Behavior Disorders, Psychosom. Med. **4**:140-149, 1942.

Kalinowsky and Putnam [3] found improvement in half of a group of 60 psychotic adults with the use of diphenylhydantoin, the patients tending to relapse when the drug was withdrawn. They suggested that diphenylhydantoin had its rationale in altering, in some way, the pathologicochemical nature of the psychosis, rather than in its anticonvulsant properties. Other reports of moderately good to excellent results in the treatment of delinquent and problem children with diphenylhydantoin on a residential and outpatient basis can be found.[4]

Hall [5] reported some success in the treatment of 10 psychotic adults with another anticonvulsant drug, trimethadione U.S.P. (tridione®). No reports on the use in psychiatric problems of one of the newer hydantoins, methylphenylethylhydantoin (mesantoin®), could be discovered in the literature. In view of the seemingly obvious rationale for the use of anticonvulsant drugs in conditions in which electroencephalographic abnormalities are to be found, it is surprising that reports have been so few. Those that have been published show, almost uniformly, beneficial results from the administration of such drugs. I believe, therefore, that this study, although performed a number of years ago, may be of value to students in the field.

TABLE 1.—*Diagnoses of Children Included in Study*

Primary behavior disorder	
Conduct disturbance	8
Neurotic traits	6
Psychopathic personality	2
Post-traumatic personality disorder	2
Postencephalitic personality disorder	2
Idiopathic epilepsy	1

PROCEDURE OF STUDY

During the first year after the inception of the children's ward at the Neuropsychiatric Institute, in June 1946, all children admitted to the ward and found to have electroencephalographic abnormalities received one or more of the anticonvulsant drugs. Soon after admission, each child (all boys), as part of the routine examination, was studied electroencephalographically, after reassurance by the other children and the personnel as to the harmlessness of the procedure, and only after his consent had been secured. Study also included an anamnesis, determinations of the physical and mental status, urinalysis, serological studies, psychological evaluation of intelligence and personality and any further specialized examination deemed necessary.

Twenty-one boys, from 6 to 13 years of age, were found to present varying degrees of abnormality, ranging from minor atypical features to gross disturbances. Although all of them presented behavior patterns unacceptable in the community or home, and necessitating hospitalization, the diagnoses varied considerably (table 1). At least four of the children with the diagnosis of primary behavior disorder had organic components of undetermined origin complicating or causative of their disturbance.

The single criterion for inclusion in this study was electroencephalographic abnormality, no matter what the nosologic impression was. Workers in the field are aware of the imprecise character of the diagnostic categories in child psychiatry and of how difficult it is to establish a definite diagnosis when all the variables must be considered. These children exhibited, on the

3. Kalinowsky, L. B., and Putnam, T. J.: Attempts at Treatment of Schizophrenia and Other Nonepileptic Psychoses with Dilantin, Arch. Neurol. & Psychiat. **49**:414-420 (March) 1943.

4. Brown, W. T., and Solomon, C. I.: Delinquency and the Electroencephalograph, Am. J. Psychiat. **98**:499-503, 1942. Walker, C. F., and Kirkpatrick, B. B.: Dilantin Treatment for Behavior Problem Children with Abnormal Electroencephalograms, ibid. **103**:484-492, 1947.

5. Hall, E. P.: Observations on the Use of Tridione in Disturbed Psychotics, J. Ment. Sc. **94**:733-736, 1948.

whole, rather severe disorders. This was thought to be of advantage in evaluating therapy, since changes would be more easily quantifiable and there would be less possibility of the occurrence of spontaneous remissions often seen in less disturbed children who have had any form of therapy.

During the patient's hospitalization rather extensive behavior charts were kept, in addition to the usual psychiatric nursing notes. The patient's day was divided into a number of functional periods, and each person with the child during that time independently evaluated his behavior as unchanged, worse or improved. Unfortunately, it was not possible to have these observations made with complete independence, since at the time of ward conferences, when each child's behavior was discussed and integration of the therapeutic regimen attempted, the personnel perforce became acquainted with the opinions of others about the child's progress. In addition, records of progress were not locked up and could very well have been consulted by some personnel members, with consequent influence on their evaluations. At least 20 daily notes by a minimum of five observers, including nurses, physicians and occupational therapists, resulted in a fairly objective check on the child's behavioral status, deemed necessary in the evaluation of any therapy. It was interesting to note that the correlation of observations by various personnel members was high, an agreement considered most useful in judgment.

The general procedure in this study was to permit each child a period of adjustment to the ward and personnel, so that what was thought to be a basal level of behavior was reached before drugs were administered. This period varied from two to eight weeks. Diphenylhydantoin sodium was then given, beginning with 100 mg. twice or three times a day, the amount depending roughly on the patient's age and weight. The dose was gradually increased until signs of toxicity were observed or a sufficiently high level was deemed to have been reached. When toxic symptoms appeared, the dose was decreased until they disappeared and was then maintained at that level. In only two cases was it necessary to halt administration of diphenylhydantoin in less than three weeks (minimum time of administration) because of toxicity, and in one of these (case 12) the patient exhibited some improvement in behavior, which was confirmed when he was on mesantoin® therapy. Minimum and maximum daily doses were 0.05 and 0.67 Gm., respectively.

Other anticonvulsant drugs were administered similarly, the dosage depending on the length of the patient's hospitalization and other problems of ward and patient management. Eleven children received mesantoin® in doses of from 150 to 400 mg. daily. Ten patients were placed on trimethadione in amounts of from 300 to 980 mg. per day. Six boys received 45 to 195 mg. of phenobarbital as the total daily amount. Ten patients were finally placed on amphetamine medication, not only as part of the total therapeutic program of the ward for these children but as a control on the observations of the personnel, since previous experience had indicated that a large percentage of patients of the type studied could be expected to respond with overt improvement.

Because of our method of administering the drugs, a rather large number of toxic reactions were encountered. Seven boys exhibited toxicity to diphenylhydantoin, five having the common, measles-like rash; three had ataxia; two had, in addition, nausea and vomiting, and one of these displayed nystagmus. One of the children who had a rash, fever, ataxia and lethargy while receiving diphenylhydantoin exhibited precisely similar symptoms with mesantoin.® No other toxic manifestations were observed with the use of mesantoin® or any of the other drugs used in this study except for the almost universally observed loss of appetite during amphetamine medication.

Soon after the beginning of our study we found that it had become a matter of prestige among the children to receive medication, and we found it necessary to supply most patients with some kind of pill. We used vitamin preparations for those children who at any time were not receiving anticonvulsants. We did not discourage these demands by the boys, since, with the entire ward population on some form of medication, a type of placebo control was automatically established. It also diminished considerably any difficulty in securing patients' cooperation in taking the drugs.

When the observations of the various ward personnel which had been noted more or less independently were reviewed for each child, a surprisingly high consensus was discovered. In only one instance (case 11) was there a significant degree of variation of opinion, and there the amount of improvement noted by some was slight. In all cases, without exception, when improvement was noted with drug therapy it was observed within a week. Since improvement of

behavior was seen in a large number of the patients and could be attributed to any number of factors inherent in residential treatment of children, no improvement was attributed to administration of drugs unless there was a diminution of improvement within a reasonable time on withdrawal of the drug. Return to former levels of behavior following cessation of anticonvulsant therapy in those cases in which the condition was deemed improved under drug therapy was seen within three days. A second trial of the same drug was then usually performed in order to confirm our original impression.

The histories of the children which follow contain the barest necessary summary of the significant findings. The presenting complaint, history of present illness, family history, physical status, including the electroencephalographic findings, diagnosis, medication and disposition are noted, in that order. The doses of drugs given are the maximums administered to the individual boy. It was frequently necessary to reduce the given dose at some time in the course of study.

REPORT OF CASES

CASE 1.—The patient, aged 8 years, was hyperactive, destructive and negativistic. He had temper tantrums, headaches, dizzy spells, insomnia, nightmares and enuresis and was unable to make friends. His symptoms dated from the first skull fracture, at the age of 5 years. A second fracture was sustained at the age of 6. School grades remained good, but adjustment gradually deteriorated. He was an affectionate child, attached to his mother, and overreacted emotionally.

The father, a psychopath, had served three prison sentences and was finally divorced by the mother. The mother and six siblings were relatively well adjusted. The family was insecure economically.

The form of the electroencephalogram was poor because of superimposed low voltage, sharp, fast activity; alpha waves, with a frequency of 8½ to 9 per second, made 20 per cent of the record; dominant slow waves, with a frequency of 6 to 7½ per second, constituted 60 to 70 per cent, with some 4 to 5 per second activity and some spiky waves. The hyperventilation effect was pronounced and was reached in 30 seconds; it consisted of high voltage 5 to 6 per second activity, continuing as 3 to 4 per second waves. The electroencephalogram showed disorganization and was definitely abnormal, suggesting generalized cerebral damage. There was no localization.

The second electroencephalogram, taken during diphenylhydantoin medication, revealed no definite improvement.

The Stanford-Binet intelligence quotient was 115. In the ward the patient was seclusive and disorganized, with short attention span.

The diagnosis was post-traumatic personality disorder.

Administration of diphenylhydantoin, up to 300 mg. daily for six weeks, and of mesantoin,® up to 300 mg. daily for three weeks, produced no improvement. With amphetamine sulfate, up to 20 mg. daily for three weeks, and *d*-amphetamine sulfate (dexedrine®), 35 mg. daily for four weeks, his condition greatly improved.

The patient was discharged home as showing improvement only when receiving amphetamine.

CASE 2.—The patient, aged 8 years, was unresponsive and defiant. A cord was found embedded in the penis, placed by the patient prior to his admission to prevent enuresis. He had been committed to the care of the state because of the mother's neglect and rejection, after having been transferred from many foster homes because of unsatisfactory behavior.

The mother was promiscuous; the patient was probably illegitimate. The parents were divorced; the father was later killed in action.

Alpha waves, 9 to 10 per second, amounted to more than 70 per cent of the record from the occipital regions, with some 3 to 4 per second and 1 per second activity. In the motor regions there was a preponderance of 5 to 6 per second activity, with some 4½ per second discharges and spiky waves. The hyperventilation effect was marked, appearing after 10 seconds and disappearing slowly; it consisted mostly of high voltage 5 to 6 per second waves. The record was clearly abnormal and was suggestive of a congenital anomaly or some type of cerebral damage.

In the ward the boy was aggressive, destructive, excitable and tense.

The diagnosis was primary behavior disorder, conduct disturbance.

With diphenylhydantoin sodium, 300 mg. daily, a rash developed, and the dose was reduced. His behavior became worse, improving after cessation of the drug. Trimethadione, 300 mg. daily for three weeks, made the behavior worse. Administration of amphetamine sulfate, 25 mg. for three weeks, was followed by obvious improvement.

The patient was discharged as decidedly improved.

Case 3.—The patient, aged 7 years, presented a feeding problem and had asthma. He was aggressive, hyperactive, confused, preoccupied and inaccessible, with marked affect hunger and inability to concentrate in school. He was destructive, with short attention span.

He had been totally rejected by his parents, receiving severe physical abuse and sustaining as a consequence numerous fractured bones and burns. He exhibited rickets and retardation in development. He had been removed from his home at the age of 3 by legal action and criminal indictment of his parents and was placed in the home of a fundamentalist minister, where he received rigid care without understanding and little affection. He was finally rejected by his foster parents, who deserted the child by leaving the state and returning him unceremoniously to the supervising agency.

Physical examination revealed many scars from burns and signs of old rickets.

The electroencephalogram showed only a few noticeable stretches of alpha activity; the dominant activity was slow, 4 to 7 per second waves. The hyperventilation effect was rapid and striking, with numerous 4 to 5 per second waves of extremely high voltage. The record was clearly abnormal and definitely epileptoid.

The second electroencephalogram, taken during therapy, revealed no change.

The intelligence quotients, variously reported, ranged from 78 to 106. In the hospital the Cornell-Coxe intelligence quotient was 113. In the ward he was easily frustrated, negativistic and affectionate; his behavior gradually improved.

The diagnosis was primary behavior disorder, with neurotic traits.

Diphenylhydantoin sodium, up to 200 mg. daily for two weeks, resulted in rash, fever, lethargy and ataxia, with no improvement in behavior; a smaller dose, given later, resulted in the same toxic symptoms, with no improvement. Mesantoin,® up to 150 mg. daily, produced similar toxic symptoms after two weeks, with questionable improvement in behavior. Trimethadione, 450 mg. daily for two weeks, produced no improvement. Amphetamine sulfate, 25 mg. daily for four weeks, led to obvious improvement.

He was discharged to a foster home, where the improvement continued.

Case 4.—The patient, aged 10, was uncooperative, hyperactive, destructive and aggressive. He had been expelled from school and was enuretic. He was born one month prematurely and had severe pertussis at the age of 8 months. Grand mal seizures developed at the age of 8 years, changing after a few months to psychomotor attacks. These seizures were characterized by an aura of fear, followed by a short period of aimless rapid running, with amnesia for the seizure. The frequency of attacks was up to eight daily, and there was occasional incontinence. Behavior difficulties dated from the onset of epilepsy.

The father was irritable, enuretic and rejecting; the mother was overprotective. She had had three stillborn premature deliveries. The patient showed rivalry with his normal brother but had a good relationship with his sister.

Physical examination revealed nothing abnormal except for numerous scattered minor scars.

The electroencephalogram revealed sporadic 8½ to 9 per second activity in the occipital regions; the record was otherwise similar to that of the motor areas, where dominant activity was 5 to 6 per second with some 4 per second waves. On hyperventilation, high voltage 4 to 6 per second waves were seen. The record was definitely abnormal, particularly in the motor regions and was compatible with that of a convulsive disorder.

The Stanford-Binet intelligence quotient was 104.

The diagnosis was idiopathic epilepsy, with grand mal and psychomotor seizures.

Under treatment with trimethadione, 600 mg. daily, to which later were added diphenylhydantoin sodium, 200 mg., and phenobarbital, seizures were notably decreased, but the disorganized behavior continued unchanged. On trimethadione therapy alone modified grand mal seizures were precipitated.

The patient was discharged unimproved to a state school for epileptics.

CASE 5.—The patient, aged 13, was negativistic, given to explosive outbursts, obscene, aggressive and destructive.

The father had been alcoholic and assaultive and had rejected the patient; he was found drowned when the patient was 9 years old. The mother was syphilitic, promiscuous and alcoholic; she died when the patient was 11 years old. One brother was well adjusted; one sister was syphilitic but well adjusted.

Repeated serologic tests for syphilis gave negative results. The cerebrospinal fluid was normal.

The electroencephalogram showed over-all abnormality, with poor organization, numerous slow, 2 to 3 per second activity and a tendency toward high voltage. The record was distinctly abnormal.

The Stanford-Binet intelligence quotient was 81. The intelligence quotient on the Arthur performance test was 97. The patient never adjusted to the ward. He had no foresight or remorse and formed no attachments.

The diagnosis was psychopathic personality.

Diphenylhydantoin, 450 mg. daily for nine weeks, and mesantoin,* 450 mg. daily for seven weeks, produced no improvement.

The patient was discharged unimproved to a state hospital.

CASE 6.—The patient, aged 10 years, was destructive, markedly hyperactive and disorganized, with a short attention span; he had been expelled from school. The symptoms dated from infancy. He was placed in a school for epileptics, with some improvement in behavior. The mother was tense and oversolicitous but furnished the patient adequate care.

The electroencephalogram showed a moderately large proportion of 9 to 10 per second, irregular activity, with poor amplitude and modulation. There were a large proportion of serial and single 5 to 6 per second waves and occasional bursts of 3 to 4 per second waves with dicrotic notches. The hyperventilation effect was moderate to marked, consisting of 5 to 6 and 2 to 3 per second waves, with a great rise in voltage. There were some definite spike and wave activity and some normal features, mixed with rather abnormal characteristics. The record was indicative of an epileptic process of psychomotor type.

The intelligence quotient on the Stanford-Binet test was 86.

The diagnosis was primary behavior disorder, conduct disturbance, with undetermined organic components.

Under treatment with diphenylhydantoin, up to 500 mg. daily, the patient had nausea, vomiting and ataxia, with no improvement when the dose was reduced to the point of tolerance. Amphetamine sulfate, 20 mg., resulted in no improvement. The patient remained in the hospital for only a few weeks; medication was continued at home, with no improvement.

CASE 7.—The patient, aged 7 years, was restless and hyperactive, with temper tantrums. He had been expelled from school because of sexual advances on schoolmates. He presented a speech defect. The symptoms followed a severe illness of two weeks, from which he emerged with strabismus. At the age of 3 years, he had apparently been seduced by a maid, and his interest in female genitalia dated from that time.

The father, deceased, had previously been divorced by an unstable, promiscuous mother, who had been married three times. The stepfather was understanding, warm and affectionate, and the patient was very fond of him. The home was financially insecure.

The electroencephalogram showed no normal alpha waves but was dominated by 5½ to 6 per second, high voltage, irregular activity with some fast components superimposed. A marked hyperventilation effect appeared after 20 seconds, and consisted of smoother 4 to 4½ per second waves. The record was strikingly abnormal, suggestive of a damaged or underdeveloped brain.

The Stanford-Binet intelligence quotient was 86.

In the ward the patient was seclusive, intermittently affectionate and perseverative; he sustained a basal skull fracture during a hyperkinetic episode, recovering without obvious sequelae.

The diagnosis was postencephalitic personality disorder.

Administration of diphenylhydantoin sodium, up to 200 mg. daily for three weeks, resulted in no improvement. Trimethadione, 300 mg. daily for three weeks, produced no improvement. Phenobarbital, 45 mg., daily for six weeks, resulted in slight improvement. With amphetamine sulfate, in varying doses up to 20 mg. daily, he was definitely worse.

He was discharged home somewhat improved.

CASE 8.—The patient, aged 11 years, presented hyperactivity and irritability, truancy, difficulty in concentration, fear of dying and complaints of paralysis; he stole and had been expelled from school because of aggressiveness. The hyperactivity and disorganization had existed prior to skull fracture at the age of 1 year. He had been placed in an orphan asylum from 7 to 10 years of age.

The father, a psychopath, with a number of criminal prison sentences, had been divorced by the highly neurotic mother after severe marital discord.

The electroencephalogram showed irregular frequency and amplitude modulation, numerous spiky waves and numerous single 2, 3 to 4, and 5 to 6 per second waves, with some serial activity. The hyperventilation effect was moderate, with many high voltage, single 3, 4 and 5 per second waves. The frontal regions showed 50 to 60 microvolt, 14 to 15 per second activity. The record showed general disorganization and was suggestive of epilepsy.

In the ward the patient exhibited homosexual activity, neurotic headaches and a high degree of suggestibility.

The diagnosis was primary behavior disorder, neurotic traits, with possible complicating post-traumatic personality features.

Diphenylhydantoin sodium, 200 mg. daily for four weeks, produced no change. Mesantoin,® 300 mg. daily for four weeks, resulted in no improvement.

He was discharged home slightly improved.

CASE 9.—The patient, aged 9 years, was encopretic, aggressive and masochistic; he was subject to temper tantrums, was retarded, had attempted to kill his siblings and was unable to adjust to school. His symptoms dated from a severe illness with coma at 3 years of age, from which he emerged with strabismus.

The father was moderately alcoholic; the six siblings had normal histories.

The electroencephalogram showed poor amplitude and frequency modulation, a large proportion of 9 to 10 per second, irregular alpha waves, a large proportion of 7 to 8 per second activity, numerous spiky waves, much slow wave irregularity and mild bursts of 2 to 3 per second activity. Hyperventilation had a strong effect, resulting quickly in 5 to 6 per second, highly irregular waves. The record was definitely abnormal, with epileptoid characteristics, consistent with postencephalitic damage.

In the ward the patient was, in addition, fearful, hyperactive, impulsive, destructive and cruel.

The diagnosis was postencephalitic personality disorder.

Treatment with diphenylhydantoin sodium, 300 mg. daily for three weeks, produced no change. Mesantoin,® 450 mg. daily for three weeks, caused no improvement. On administration of trimethadione, 600 mg. daily for two weeks, he showed obvious improvement, the improvement disappearing on interruption of medication and reappearing on resumption of the drug. With amphetamine, 20 mg. daily for one week, his behavior became worse.

He was discharged to a state hospital as slightly improved.

CASE 10.—The patient, aged 9 years, was hyperactive, disorganized, aggressive, destructive, excitable and impulsive; he was subject to sleepwalking, nightmares and temper tantrums, made sexual advances to his mother and half-sister and had been expelled from school because of inability to adjust.

The patient was born after a prolonged three day labor, after permission for cesarean section had been denied by the grandfather. He presented signs of birth injury, including a prolonged startle pattern during infancy. He was placed in a foster home soon after birth, from which he was removed at the age of 2 years because of completely unacceptable behavior, which continued after he was taken into his mother's home.

The patient was illegitimate; the mother was neurotic; the stepfather had rejected the patient when his own child was born, and the parents then separated.

In the electroencephalogram, 9 per second activity constituted 30 per cent of the record from the occipital regions and was completely lacking in the motor regions; the dominant activity, 5 to 6 per second and irregular, amounted to 60 to 80 per cent of the record. The hyperventilation effect was marked and was achieved in 10 to 15 seconds, consisting of 3½ per second waves. The record was clearly abnormal, being highly suggestive of a damaged and/or undeveloped brain, probably the former.

In the ward the boy was distractible and superficial in affect, exhibiting extremely poor judgment.

The diagnosis was post-traumatic personality disorder.

Diphenylhydantoin, 700 mg. daily for four weeks, made the behavior worse; trimethadione, given for two weeks, produced no change. Phenobarbital, 200 mg. daily for three weeks, resulted in obvious improvement. Amphetamine, 20 mg. daily for one week, produced no change.

He was discharged unimproved, except with phenobarbital, to state hospital care.

CASE 11.—The patient, aged 9 years, exhibited feminine attitudes and interests. He was restless, impulsive, tense and insensitive to trauma. Lying, disobedience and poor adjustment were noted at school.

He had shown a strong interest in feminine pursuits and feminine speech and mannerisms from the age of 3 years. He made friends only with girls. His scholastic grades were good.

The parents had separated, been divorced and remarried. The father was alcoholic, easy going and affectionate. The mother had wanted a girl prior to the birth of the patient. The patient showed rivalry with his older brother; he was fond of a 5 year old sister, whom he took care of and dressed.

Alpha waves (8½ to 9 per second) formed 60 per cent of the record. The tracings from the occipital regions were more abnormal, 1 to 2 per second activity constituting 40 to 50 per cent and 5 to 6 per second waves forming 20 to 25 per cent of the record. Frequency and amplitude modulation was poor. There was some abortive spike and wave activity. The hyperventilation effect was marked and was reached after 30 seconds. It consisted of extremely high voltage 3 to 4 per second and then 2 to 2½ per second activity. Some paroxysmal psychomotor seizure patterning was evident. The record was definitely abnormal, showing a great deal of disorganization and damage.

The Stanford-Binet intelligence quotient was 108.

In the ward the patient was eventually well accepted by the boys and was more affectionate. His effeminate behavior practically disappeared.

The diagnosis was primary behavior disorder, with neurotic traits.

Diphenylhydantoin sodium, 300 mg. daily for three weeks, produced a toxic rash, with no change in behavior. Mesantoin,* 300 mg. daily for three weeks, resulted in no improvement.

He was discharged home, much improved.

CASE 12.—The patient, aged 9 years, was restless, moody, overactive, impulsive, irritable and destructive; he had temper tantrums, played truant, had a speech defect, was rejected by other children and had been expelled from school because of inability to adjust. He had presented a behavior problem since the age of 3.

Both parents were mentally defective. The mother had a severe speech defect. The neighborhood and home were extremely poor. The patient was the youngest of four siblings and was by far the most intelligent member of the family. One sibling was dead; another was living with relatives; a third was uncommunicative.

Alpha waves (10 per second) constituted 80 to 85 per cent of the electroencephalogram. Some 6 to 5 per second activity was shown, especially in the temporomotor area, as well as some 3 to 4 per second waves and minor atypical features. The electroencephalogram was not definitely outside normal limits.

The Stanford-Binet intelligence quotient was 96. Speech improved with therapy.

The diagnosis was primary behavior disorder, conduct disturbance.

Diphenylhydantoin, 300 mg. daily for three weeks, produced some improvement; mesantoin,* 300 mg. daily for three weeks, resulted in obvious improvement within three days, which was lost when intake of the drug was stopped.

The patient was discharged, much improved.

CASE 13.—The patient, aged 12 years, was given to stealing, was obscene and aggressive, indulged in homoerotic practices and had school difficulties. He was placed in an orphan asylum soon after birth, where he remained until 9 years of age, and was then transferred to the home of his father, who had remarried. One convulsion was reported to have occurred prior to admission.

The mother was epileptic and was confined to a state hospital in a deteriorated state soon after the birth of the patient. The father was unstable and rejected the child.

The electroencephalogram showed poor frequency and amplitude modulation, dominated by 7 to 8 per second activity with dicrotic notches. There was more irregularity in the motor than in the occipital areas, many high voltage, spiky waves. The hyperventilation effect was mild, with a few abortive spike and wave patterns. The record was mildly abnormal, suggesting epilepsy.

A second electroencephalogram, taken during diphenylhydantoin therapy, showed lowering of alpha activity and increase in both fast and slow components. The record showed increased abnormality:

The pitressin® hydration test gave a negative result.

The Stanford-Binet intelligence quotient was 102.

The diagnosis was primary behavior disorder, conduct disturbance.

Diphenylhydantoin, 300 mg. daily for 10 weeks, produced no improvement.

He was discharged to an institution for care of normal children, where satisfactory improvement continued.

CASE 14.—The patient, aged 12 years, was given to truancy and stealing and was destructive, aggressive, enuretic, obscene and cruel to animals. He had been committed to state care, having failed to adjust in a number of good foster homes.

The mother died when the patient was 4 years old. The father was a severe disciplinarian and rejected the child. The patient had six siblings, one of whom was in a state training school for delinquent girls.

The occipital regions presented a large proportion of 9½ per second alpha waves. The record from the motor regions was much more abnormal, with a large proportion of 5 to 6 per second activity and many clearly diphasic spikes of extremely high voltage; alpha activity was mostly absent. The hyperventilation effect was pronounced, being characterized by a great rise in voltage, 5 to 6 per second waves, followed by 3 to 4 per second waves, and many abortive spikes and waves. The electroencephalogram was definitely abnormal, with noticeable epileptic features.

The Stanford-Binet intelligence quotient was 85.

The diagnosis was primary behavior disorder, conduct disturbance.

Diphenylhydantoin sodium, 300 mg. daily for three weeks, produced no improvement.

The patient was discharged to an institution for care of normal children, unimproved.

CASE 15.—The patient, aged 12, had presented a behavior problem from early childhood, characterized by stealing, lying, sexual activity with animals and younger children, cruelty to animals and aggressiveness.

He had failed to adjust in school from the outset and had become the neighborhood delinquent. After his mother's death he was placed with various relatives, who found his behavior unacceptable. Placement with the father resulted in brutal mismanagement, followed by a series of unsatisfactory experiences in foster and detention homes, with a final sentence to reform school.

The father, a psychopath, was cruel and alcoholic and had deserted his family. The mother, who had been alcoholic and promiscuous, and constantly ill since the patient's birth, died three years before the patient's admission.

The electroencephalogram showed irregular amplitude modulation with a dominant frequency of 9 to 9½ per second. Greater irregularity was found in the occipital than in the motor areas, where 5 to 6 per second, medium voltage activity occurred. Some 4 per second waves appeared in the temporomotor regions. The hyperventilation effect was pronounced, with high voltage 5 to 6 per second activity, some spiky waves, numerous spike and wave patterns and some 3 to 4 per second activity. Normal alpha activity was mixed with abnormal signs of epilepsy.

The Stanford-Binet intelligence quotient was 81.

The diagnosis was psychopathic personality.

The patient failed to adjust to the ward; he was preoccupied with his body, was sullen and hostile and showed no regret.

Diphenylhydantoin, 300 mg. daily for three weeks, and mesantoin,® 400 mg. daily for four weeks, produced no improvement. Trimethadione, 980 mg. daily for two weeks, made the behavior definitely worse. The drugs produced no signs of toxicity.

He was discharged and returned to the reform school unimproved.

CASE 16.—The patient, aged 6 years, was unresponsive and enuretic; his behavior was characterized by nail biting, vomiting, teeth grinding, nightmares, temper tantrums, masturbation and speech defect. He had been placed in a number of foster homes, where he received inconsistent, rejecting care and showed increasing negativism, excitability, destructiveness, sexual aggressivity and homicidal assaults. Finally, he was placed in an orphan asylum, where the "personnel was made ill by his behavior."

The father, with paranoid schizophrenia, was confined to a state hospital. The mother, who was mentally defective and promiscuous, had been married three times and had rejected the child. The patient was also rejected by four fairly well adjusted siblings.

The electroencephalogram showed a general frequency of 5 to 6 per second, with superimposed very low voltage, high frequency 20 to 30 per second waves, and sometimes uncountable activity. The hyperventilation effect, appearing in 10 seconds, showed a sudden rise in voltage and smooth 5 per second waves. The electroencephalogram was definitely abnormal, with little alpha activity.

The Stanford-Binet intelligence quotient was 101.

In the ward the boy was sullen, withdrawn, hostile, disorganized and explosive for weeks, with final gradual improvement in all aspects, including speech.

The diagnosis was primary behavior disorder, with neurotic traits.

Use of diphenylhydantoin, up to 300 mg. daily for five weeks, produced a toxic rash, which disappeared on lowering the dose. There was no improvement in behavior.

The patient was discharged to a foster home, where excellent improvement continues.

CASE 17.—The patient, aged 10 years, was irritable, aggressive, tense and restless, with temper outbursts and severe reading and writing disability. The difficulties dated from the time of school placement, with progressive increase in symptoms. The child was left handed.

The father was driving and energetic; the mother was passive and overprotective. The child had four siblings—two well adjusted and two tense and irritable.

Seventy per cent of the electrocephalogram consisted of 7 per second, high voltage activity and some 1 to 2 and 3 per second waves. Hyperventilation definitely raised the voltage and slowed the frequency 1 to 1½ cycles per second. The record was abnormal, suggesting a diffuse condition, metabolic or developmental in character.

The Stanford-Binet intelligence quotient was 96.

The diagnosis was primary behavior disorder, conduct disturbance.

Diphenylhydantoin, 300 mg. daily for four weeks, produced no improvement.

He was discharged home to continue improvement on remedial school teaching.

CASE 18.—The patient, aged 11 years, presented enuresis, destructiveness, inability to learn and fire setting. He was committed to state care because he was neglected by his parents. He failed to adjust in foster homes and in an institution for care of normal children.

The parents were of low intelligence and inadequate; the mother died when the patient was 3½ years old. The siblings were of borderline intelligence.

The electroencephalogram showed a basic frequency of 6 to 7 per second, high voltage, irregular waves, with a small amount of 8½ per second alpha waves, numerous spiky and fast (14 to 17 per second) components and many single 3 to 4 per second waves. The hyperventilation effect was marked and prolonged, with 3 to 6 per second abortive spike and wave activity. The record was highly abnormal, suggestive of a damaged brain, with some epileptoid function.

The Stanford-Binet intelligence quotient was 65; the Cornell-Coxe intelligence score, 81.

In the ward he was affection hungry, anxious, lacking in self confidence, with numerous somatic complaints and good deal of fantasy formation.

The diagnosis was primary behavior disorder, with neurotic traits.

Diphenylhydantoin, 300 mg. daily for three weeks, and mesantoin,® 300 mg. daily for three weeks, produced no improvement.

He was discharged to a state school slightly improved.

CASE 19.—The patient, aged 9 years, was enuretic, destructive, hyperactive and unable to dress himself or to tie his shoe laces. One typical epileptic seizure was reported. After desertion by his mother, he was rejected by his uncle and failed to adjust in 10 different foster homes.

The father was shiftless and alcoholic; the mother had deserted the family. Two siblings were making fairly good adjustment in foster homes.

Physical examination revealed generalized clumsiness, a fine tremor of the upper extremities and adiadokokinesis.

The electroencephalogram showed a dominant frequency of 7 to 8 per second, quite a few high voltage 3 to 4 per second spiky waves with dicrotic notches and a few abortive spike and wave formations, with occasional 3 to 4 per second activity on the left side. Hyperventilation effect was moderate, with quite a few slow waves. The record was highly abnormal, compatible with a mixed type of epileptic process, of psychomotor and petit mal character.

A second electroencephalogram during diphenylhydantoin therapy revealed no change.

In the ward the patient exhibited marked disorganization in all spheres of behavior. He was insecure and anxious, with acute feelings of inferiority. He showed a speech defect in relation to periods of emotional stress, with stuttering and blocking. The head rolling which he exhibited prior to falling asleep disappeared during diphenylhydantoin therapy and reappeared when the drug was discontinued.

The diagnosis was primary behavior disorder, neurotic traits, with an undetermined organic component.

Diphenylhydantoin, 200 mg. daily for five weeks, produced a rash, and the behavior symptoms became definitely worse. Mesantoin,® 200 mg. daily for three weeks, made the behavior worse. Trimethadione, 300 mg., produced no change. Phenobarbital for four weeks and amphetamine for two weeks produced no improvement.

The patient was discharged to a state school for epileptics unimproved.

CASE 20.—The patient, aged 6 years, was extremely hyperkinetic, autistic, impulsive, destructive and cold, with limited attention span, and was excluded from school. His symptoms dated from infancy.

The child was illegitimate; the father was unknown; the mother was young and of superior intelligence. The child was adopted by intelligent, middle class parents, who gave the patient excellent, warm care.

The electroencephalogram showed a prevailing frequency of 6 to 7 per second, with poor amplitude and frequency modulation, rare alpha waves and 7 to 4 per second activity in the temporomotor areas. Hyperventilation produced some rise in voltage and slowing of waves. The record showed mild generalized disorganization and abnormality in cerebral activity, not clearly diagnostic of any epileptic function, although some epileptoid characteristics were present.

The second electroencephalogram, taken during amphetamine therapy, showed some improvement. Alpha waves were better formed, probably owing to medication. There was some assymmetry in recording from the left motor-occipital area.

The Stanford-Binet intelligence quotient was 143.

The diagnosis was primary behavior disorder, conduct disturbance of undetermined organic nature.

Diphenylhydantoin, given up to 300 mg. daily for five weeks, produced nausea, ataxia, vomiting and nystagmus, with no improvement in behavior at any time. Mesantoin,® 300 mg. daily for two weeks, produced no change. Trimethadione, given for three weeks, resulted in no improvement. Phenobarbital, up to 128 mg., made the behavior definitely worse. Under treatment with amphetamine, 20 mg. daily for five weeks, the child showed striking and dramatic improvement and became quiet and affectionate.

The child was discharged as showing improvement only on amphetamine therapy.

CASE 21.—The patient, aged 13, was aggressive, destructive, dull, unable to make friends, disorganized and day dreaming. Failing to adjust in many foster homes, he was placed in a state school for defective children at 2½ years of age. There behavior gradually improved to the point where placement in a foster home was finally accomplished, at the age of 6 years.

The boy was illegitimate; his parents were unknown.

The electroencephalogram was characterized by poor amplitude and frequency modulation; alpha waves were much less in evidence in the motor regions; there was a large proportion of single 3 to 4 per second waves and serials of 4 to 6 per second waves, numerous dicrotic waves, and many 3 to 4 per second waves with sawtooth tops, the left side being probably slightly more abnormal. The hyperventilation effect was moderate to marked, with numerous single 3 to 4 per second waves. The record was clearly abnormal, with signs of an epileptic process, with emphasis on psychomotor components, and evidence of generalized disorganization.

The Stanford-Binet intelligence quotient was 81.

The diagnosis was primary behavior disorder, conduct disturbance.

Diphenylhydantoin, 300 mg. daily for three weeks, produced no change. Trimethadione, in doses up to 900 mg. daily for five weeks, had no effect. Phenobarbital, 300 mg. daily for three weeks, made the behavior worse. Amphetamine sulfate, 20 mg. for one week, made the behavior worse.

The patient was discharged to his previous foster home, slightly improved.

RESULTS

As can be seen from table 2, our results with some of the common anticonvulsant drugs were almost uniformly disappointing. Only one boy exhibited slight improvement with diphenylhydantoin; four were made worse by the drug. The same patient displayed obvious improvement while receiving mesantoin,[6] and in another questionable slight improvement was observed. Of nine boys placed on trimeth-

TABLE 2.—*Behavior Following Administration of Drugs* *

Case	Diphenyl-hydantoin Sodium	Mesantoin[6]	Trimeth-adione	Pheno-barbital	Amphet-amine
1	0	0	..	..	+++
2	—	..	—	..	++
3	0	+?	0	..	++
4	0	..	0	0	..
5	0	0	..	..	..
6	0	..	..	..	0
7	0	..	0	+	—
8	0	0	..	..	..
9	0	0	++	..	—
10	—	..	0	++	0
11	0	0	..	..	..
12	+	++	..	..	..
13	0	..	..	..	..
14	0	..	..	..	..
15	—	0	—	..	..
16	0	..	..	..	..
17	0	..	..	..	..
18	0	0	..	..	..
19	—	—	0	0	0
20	0	0	0	—	+++
21	0	..	0	—	—

* — indicates the behavior was made worse; 0, means no change; +, slight improvement; ++, obvious improvement; +++, marked improvement, and ?, questionable result.

adione therapy, only one exhibited obvious improvement. One child receiving phenobarbital exhibited obvious improvement, and another, slight improvement. On the other hand, of 10 children receiving amphetamine, four were found to be obviously or greatly improved.

It may be of some significance that in case 12, in which the hydantoins had their most obvious effect, the patient had the most nearly normal electroencephalogram of the group. Trimethadione had its only effect in a fairly well proved case of postencephalitic personality disorder. As reported previously,[2] phenobarbital and amphetamine were found to be antagonistic clinically (cases 7 and 20). On a number of patients, a second or third electroencephalogram was taken while they were under therapy. Little or no change was observed in the record whether or not improvement was noted clinically.

COMMENT

In an area of medicine in which it is exceedingly difficult to evaluate any therapeutic regimen because of the enormous number of variables which must be considered and controlled, and in which even judgment of improvement is difficult to make objectively, particularly when value judgments, conscious or unconscious, must be made, it is incumbent on all workers in the field to be most cautious in advancing claims of therapeutic efficacy for a single procedure. The history of psychiatry is replete with methods of treatment which have had success varying up to the miraculous. It must be confessed that improvement has followed application of almost every means reported through the centuries, but the errors involved in *post hoc* thinking, lack of adequate controls and mere disregard of the statistics of significance have served frequently to make our specialty a laughingstock within the medical profession.

It would be interesting and profitable to speculate on some of the factors which are difficult to control in outpatient psychiatric therapeutic research and which are more easily delimited on a ward. Child psychiatrists have frequently observed notable improvement in their patients after a single visit to a clinic, often without anything definite having been done for child or patient. This may be attributable to a number of factors. The very decision to seek psychiatric or medical help frequently involves a distinct change in parental attitude. Inherent in the decision is a feeling that there may be "something wrong" with the child, that he may be ill and not "bad" or "mean." In the good clinic, where the parent is not made to feel guilty for what she (or he) may or may not have done to the child, with consequent self-defensive confirmation of her previous attitude of the innate evil within her child, she is strengthened in her belief in her child's illness. This alone is probably sufficient in many cases to cause a change in the parental punitive attitude toward the child, with consequent improvement in behavior on the part of the child, which may set up a reversal of the spiral of unacceptable behavior—punishment with worsening of behavior—further unacceptable behavior, so often observed as a fundamental process in conduct disorders.

Added to the ordinary clinic procedure of history taking and examination may be an impressive diagnostic program, such as the taking of an electroencephalogram, which is followed by the prescription of certain oddly striped or colored capsules or pills, which causes the druggist to look oddly on the child. It is not at all surprising that the mother is convinced that her child has sufficient organic cause to behave as he does. One does not punish or beat a sick child; many of the attitudes and poor methods of management are discarded, and improvement may thereby result. The improvement appears as confirmatory proof to the parent that her new insight is correct, and the spiral mentioned previously may undergo the desired reversal, so that the normal maturational patterns may have the necessary freedom to develop. A little leaven of self-imposed guilt arising from what the parent considered her former dubious methods of management might even contribute to the improvement.

On the other hand, it is not difficult to conceive that some harm might result in the invalidizing of a child by a guilt-ridden or error-ridden mother who was too strongly confirmed in her new belief that her child had an organic brain disturbance, or by the prevention of the institution of the proper therapeutic regimen.

It is possible that these psychodynamic factors are frequently the ones observed in the very common improvement observed in children with genuine organic disturbance who have nondisturbed parents and a minimum of environmental dislocations. Explanation of the nature of the disorder and its consequent behavioral disorganization, with guidance in management, is often sufficient to remove many of the secondary emotional difficulties which have been superimposed on the original one, and then frequently permits intrinsic compensation for the organic insult to occur, so that a more or less normal child may eventually emerge, although frequently with a lowered threshold to environmental trauma.

As an additional note on the use of amphetamine in pediatric psychiatry, it should be remarked that the drug has also been used successfully as an anticonvulsant by workers in the field of epilepsy. Its well known advantage in treatment of the behavior disorders has had no adequate rationale offered for its efficacy, but the failure, here reported, of a number of anticonvulsant drugs suggests that its direct anticonvulsant properties are not what make it useful in these conditions. From experience with its use elsewhere in the treatment of a number of brain-injured, hyperactive, disorganized children, I venture the hypothesis that one of its useful effects is the inhibition of some of the random, circular and poorly integrated stimuli tracks, secondary to minor or major lesions, which have been set off in the brain by an extrinsic or intrinsic stimulus. It is these postulated nonintegrative and disintegrating neural associations which serve hypothetically as the disorganizing factor in the behavior of children with minimal cerebral injuries, usually without neurological symptoms, and lower their threshold to environmental trauma and their ability to deal with complex problems. This would then serve as the basis for the spiraling dysfunction, discussed previously, encountered in the interaction of a damaged organism with a frustrating, nonaccepting environment. The magnitude of the behavior disturbances could therefore be greatly disproportionate to the size of the lesions, which might be microscopic in extent and histologically obscure. This is in contrast to the decrease in function following loss of functioning tissue, which could occur only in gross injuries, accompanied with neurological signs. Confirmation for this preliminary hypothesis may be found in the automaton-like behavior observed in some of the children while receiving amphetamine. Paradoxically, although these children sometimes improve, almost miraculously, in social adjustment, their psychometric functioning may decrease significantly. This may be interpreted as due to excessive cortical inhibition. Among other actions of amphetamine which may possibly be explainable in the same fashion are the abolition of appetite, probably by the central inhibition of smell and taste, interference with sleep and psychological feelings of fatigue by further selective or generalized inhibition.

It should not be considered that this study conclusively closes the doors on the possibility of the use of anticonvulsant drugs in the treatment of the behavior disorders. On the contrary, the study should be repeated, preferably with more cases than the somewhat limited number presented here. It must, however, be indicated that negative results in this type of clinical study ought to be considered more confirmatory, since when improvement does occur in a psychiatric patient it is extremely difficult to state which of the many factors was causative. Each of the new anticonvulsants, as they are presented, should be given a trial, since any adjuvant

to integration in the frequently badly disorganized child with an abnormal electroencephalogram would be gratefully received. Amphetamine has already proved its value clinically over more than a decade. Another such drug without some of its handicaps would undoubtedly be most useful.

SUMMARY

Twenty-one boys with behavior problems of varied causations, 6 to 13 years of age, with various electroencephalographic abnormalities, in residential treatment in a children's psychiatric ward, received one or more anticonvulsant drugs, including diphenylhydantoin (dilantin®), methylphenylethylhydantoin (mesantoin®), trimethadione (tridione®) and phenobarbital. Their behavior was noted fairly independently by a number of observers throughout the course of therapy. With minor exceptions, the results were almost uniformly disappointing in producing any significant improvement in behavior. An attempt is made to explain the psychodynamics involved in the improvement of behavior disorders under drug administration in outpatient use, and a hypothesis is offered for the rationale of amphetamine therapy in the behavior disorders.

Johns Hopkins University, School of Hygiene and Public Health.

Abstracts from Current Literature

Anatomy and Embryology

TOPOGRAPHY OF THE CEREBELLAR ARTERIES: ABNORMAL COURSES OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY. F. LUNDOLT, Schweiz. Arch. Neurol. u. Psychiat. **64**:329, 1949.

Normally, the posterior inferior cerebellar artery arises from the rostral portion of the vertebral artery. It extends directly backward between the rootlets of the vagus nerve to the region of the obex, from which it curves back onto the inferior surface of the corresponding cerebellar hemisphere. In three of 13 cadavers used in making anatomic preparations of the posterior cranial fossa, one or both of these vessels arose from the caudal portion of the vertebral artery, extending backward in relation to the uppermost slip of the dentate ligament between the spinal roots of the accessory nerve. In two of the preparations, only one of the posterior inferior cerebellar arteries had this anomalous origin; it extended downward to form a loop on the posterior aspect of the upper cervical portion of the spinal cord before pursuing a more or less straight upward course to the inferior margin of the rhomboid fossa. In a third preparation, both vessels were arranged in a series of coils which literally filled the cisterna cerebellomedullaris. The author comments on the danger of cisternal puncture in persons having this anomaly.

DANIELS, Denver.

Physiology and Biochemistry

EFFECT OF PROCAINE INTRAVENOUSLY ADMINISTERED ON THE CUTANEOUS PAIN THRESHOLD. R. F. KIBLER and H. W. SCHNAPER, Am. J. M. Sc. **220**:19 (Aug.) 1950.

Kibler and Schnaper investigated the analgesic properties of intravenously administered procaine, with reference to the thesis that the analgesic action is attributable to the concentration of the procaine at the site of the injured tissues. They produce a first degree burn on one forearm of each of four medical students. The skin thus prepared was tender to light pressure and unusually sensitive to pinprick. The subjects were then trained to respond to "burning" pain on the traumatized forearm and to "pricking" pain on the normal side when they were tested by the Hardy-Wolff-Goodell technique. When the hyperalgesia of the burned site was at its height, 1 Gm. of procaine hydrochloride in 500 to 1,000 cc. of isotonic sodium chloride solution was injected intravenously. During the injection, the pain threshold was elevated slightly and to almost equal degrees in the normal and the hyperalgesic area. Such alteration of pain threshold as did develop may have been due to the difficulty in concentrating that occurred in the subjects during the infusion. Shortly after the infusion was completed, the pain thresholds returned to normal, in contradiction of the claims that procaine can ease pain for five to 12 hours after the injection.

BERLIN, Chicago.

STUDIES ON OLIGOPHRENIA PHENYLPYRUVICA: I. MICROBIOLOGICAL DETERMINATION OF L- AND D-PHENYLALANINE AND OF PHENYLLACTIC ACID. B. A. PRESCOTT, E. BOREK, A. BRECHER and H. WAELSCH, J. Biol. Chem. **181**:273, 1949.

The disease oligophrenia phenylpyruvica (phenylketonuria) presents a unique opportunity for the study of the relation of amino acid metabolism to the function of the central nervous system. In this inborn error of metabolism, which is inherited as a Mendelian recessive character, mental deficiency is accompanied with faulty phenylalanine metabolism. The metabolic disturbance was first recognized by the urinary excretion of large amounts of phenylpyruvic acid. It was soon recognized, however, that the voiding of the keto acid is accompanied with an abnormally high excretion of phenylalanine and phenyl-lactic acid as well. The source of the excreted amino acid and its metabolic derivatives is probably the high concentration of phenylalanine in the blood of these subjects. A microbiological method is described for the deter-

mination of *d*- and *l*-phenylalanine and of *dl*-phenyl-lactic acid in the presence of each other and in the presence of phenylpyruvic acid. *l*-Phenylalanine was determined in the protein-free blood plasma filtrates of 17 normal subjects. In these specimens the mean concentration was 0.95 ± 0.06^2 mg. per 100 cc.; the total spread of the values was from 0.6 to 1.3 mg. per 100 cc. These results are in agreement with those of other investigators. The method described above was applied to the determination of *l*- and total phenylalanine in the plasma of subjects with oligophrenia phenylpyruvica. The results show that there was no measurable increment in bacterial growth after the conversion of the amino acid to the hydroxy acid and that, therefore, no *d*-phenylalanine was present within the limit of error of the procedure. This finding makes it appear unlikely that the metabolic error in oligophrenia phenylpyruvica involves the formation of the unnatural isomer of phenylalanine.

PAGE, Cleveland.

OXIDATIVE AND GLYCOLYTIC METABOLISM OF MINCED DAY-OLD MOUSE BRAIN IN RELATION TO PROPAGATION OF THEILER'S GD VII VIRUS. H. E. PEARSON and R. J. WINZLER, J. Biol. Chem. **181**:577, 1949.

The oxygen consumption, glucose utilization, lactic acid production and propagation of Theiler's GD VII mouse encephalomyelitis virus in minced 1 day old mouse brain have been studied. The propagation of the virus had no significant influence on the oxidative or glycolytic metabolism of the host tissue. The rate of oxidative or glycolytic metabolism of the host tissue was not of prime importance in affecting the propagation of the virus.

PAGE, Cleveland.

EFFECTS OF THEILER'S GD VII VIRUS ON P^{32} UPTAKE BY MINCED ONE-DAY-OLD MOUSE BRAIN. M. E. RAFELSON JR., R. J. WINZLER and H. E. PEARSON, J. Biol. Chem. **181**:583, 1949.

The uptake of P^{32}-labeled inorganic orthophosphate and the distribution of phosphorus in the various trichloroacetic acid-insoluble phosphate fractions of minced 1 day old mouse brain and the effect of Theiler's GD VII virus propagation have been studied. During the period of maximal rate of virus propagation the uptake of P^{32} was markedly stimulated in the phospholipid and "total protein-bound" phosphate fractions. Increased turnover in the "total protein-bound" fraction associated with virus propagation is due primarily to the increased turnover of ribonucleic acid phosphorus. Desoxyribonucleic acid-phosphorus turnover was not affected. The virus-infected tissue, as compared with the noninfected tissue, had an increased ribonucleic acid-phosphorus content and a decreased desoxyribonucleic acid-phosphorus content.

PAGE, Cleveland.

EFFECTS OF THEILER'S GD VII VIRUS ON THE INCORPORATION OF RADIOACTIVE CARBON FROM GLUCOSE INTO MINCED ONE DAY-OLD MOUSE BRAIN. M. E. RAFELSON JR., R. J. WINZLER and H. E. PEARSON, J. Biol. Chem. **181**:595, 1949.

The effects of the propagation of Theiler's GD VII strain of mouse encephalomyelitis virus on the incorporation of radioactive carbon from labeled glucose into the tissue components of minced, 1 day old mouse brain incubated for 24 hours at 35 C. have been studied. During the period of maximal virus propagation there are an increased incorporation of glucose fragments into the "protein" fraction and a decreased incorporation into the lipid fraction of virus-infected tissue, as compared with values for noninfected minces. Virus propagation had no influence on the relatively slower fixation of radioactive carbon dioxide in lipid and "protein" fractions.

PAGE, Cleveland.

INHIBITORY EFFECT OF MUSCLE ADENYLIC ACID ON ANAEROBIC GLYCOLYSIS OF BRAIN. G. R. GREENBERG, J. Biol. Chem. **181**:781, 1949.

Adenosine-5-phosphoric acid and inosine-5-phosphoric acid inhibit anaerobic glycolysis in brain preparations. This inhibition is not produced by adenosine, adenosine-3-phosphoric acid or adenosine triphosphate. The inhibitory effect of adenosine-5-phosphoric acid generally decreases

as glycolysis proceeds when the initial inhibition is not great. Hexose diphosphate added to the reaction system rapidly overcomes the inhibition by muscle adenylic acid. The possible significance of this inhibition is discussed.

PAGE, Cleveland.

INFLUENCE OF METHIONINE DEFICIENCY ON AMINO ACID METABOLISM IN THE RAT. A. E. DENTON, J. N. WILLIAMS JR. and C. A. ELVEHJEM, J. Biol. Chem. **186**:377, 1950.

Rats were forcibly fed a methionine-deficient ration, and the free amino acid contents of the liver and brain and the total amino acid contents of the urine and feces were determined. The methionine contents of the liver and urine of the methionine-deficient animals were found to be lower than those of the control animals; however, the level of methionine in the brain and feces did not appear to be altered. The arginine concentrations in the liver and brain of the methionine-deficient animals were considerably lower than those of the control animals. The methionine deficiency brought about definite changes in the free amino acid content of the liver and brain, although the changes were not as marked as might be expected. The total excretion of amino acids in the urine and feces was very nearly the same as that of the control animals.

PAGE, Cleveland.

STUDIES OF ACETAL PHOSPHOLIPIDES OF BRAIN: I. PROCEDURE OF ISOLATION OF CRYSTALLIZED ACETAL PHOSPHOLIPIDE FROM BRAIN. S. J. THANNHAUSER, NICHOLAS F. BONCODDO and GERHARD SCHMIDT, J. Biol. Chem. **188**:417, 1951.

A procedure for the isolation of crystalline acetal phospholipid from beef brain is reported. The crystallized acetal phospholipid is a saturated compound. Its physical properties are described.

PAGE, Cleveland.

STUDIES OF ACETAL PHOSPHOLIPIDES OF BRAIN: II. THE α STRUCTURE OF ACETAL PHOSPHOLIPIDE OF BRAIN. S. J. THANNHAUSER, NICHOLAS F. BONCODDO and GERHARD SCHMIDT, J. Biol. Chem. **188**:423, 1951.

Glycerylphosphorylcolamine was isolated from crystalline acetal phospholipid of the brain. Its chemical and physical properties are described. It was demonstrated by periodate titration that glycerylphosphorylcolamine derived from the acetal phospholipid obtained from brain is entrely of the α structure. It is emphasized that all natural glycerol phospholipids in which the position of the phosphoric acid has been established belong to the α series.

PAGE, Cleveland.

STUDIES OF ACETAL PHOSPHOLIPIDES OF BRAIN: III. THE FATTY ALDEHYDES PRESENT IN CRYSTALLINE ACETAL α-PHOSPHOLIPIDE OF BRAIN. S. J. THANNHAUSER, NICHOLAS F. BONCODDO and GERHARD SCHMIDT, J. Biol. Chem. **188**:427, 1951.

The fatty aldehydes present in crystalline acetal α-phospholipid (phosphatid) of brain were converted into the corresponding fatty acids. Palmitic and stearic acids were identified by high vacuum distillation of their methyl esters. The isolated crystalline acetal α-phospholipid of brain does not contain unsaturated fatty aldehydes. The amount of palmitic aldehyde in the acetal α-phospholipid is larger than that of stearic aldehyde.

PAGE, Cleveland.

CUTANEOUS THRESHOLDS FOR PAIN BEFORE AND AFTER UNILATERAL PRE-FRONTAL LOBOTOMY. H. E. KING, J. CLAUSEN and JOHN E. SCARFF, J. Nerv. & Ment. Dis. **112**:93 (Aug.) 1950.

The authors attempted to evaluate the effect of unilateral prefrontal lobotomy on the cutaneous pain threshold. Tests to determine cutaneous pain thresholds by the Hardy-Wolff-Goodell technique were performed on six nonpsychotic patients who had had unilateral lobotomies. Of this group, five who had been lobotomized had had organic pain, and one was considered to have had psychogenic pain. Of the five patients with organic pain which was relieved by lobotomy, four had postoperative lowering of the cutaneous pain threshold bilaterally, and one

had a lowered pain threshold ipsilateral to the lobotomy and an elevated pain threshold contralaterally. The patient with psychogenic pain, which was not relieved by lobotomy, had bilateral elevation of the cutaneous pain threshold. One of the patients subjected to a second lobotomy on the opposite side experienced permanent relief of pain, an additional fall in cutaneous pain threshold beyond that following the unilateral lobotomy.

BERLIN, Chicago.

NEUROGRAPHY FOLLOWING EXPERIMENTAL NERVE SUTURE AND CRUSH INJURY. J. A. EPSTEIN, D. BERMAN and I. M. TARLOV, J. Neuropath. & Exper. Neurol. **8**:419 (Oct.) 1949.

Experiments performed by Weiss and his collaborators have shown that continuity of nerve sheath pathways is essential for the normal functioning of nerve fibers. The endoneurial fluid within this system has special significance in the process of nerve regeneration, for it provides a superior growth medium for the outgrowing axons and sheath cells, in addition to possessing antifibrotic properties. Consequently, in the consideration of techniques for the repair of peripheral nerve lesions, those methods are preferable which most effectively restore the normal and anatomical relationships, including the sheath pathways. The present experimental study was undertaken in order to determine the effect of various techniques of end to end suture of peripheral nerves on the reformation of these channels. In addition, the continuity of the pathways following the infliction of crush injuries was also investigated. The sheaths were studied roentgenographically after the injection of radiopaque compounds (thorotrast®) into the perineural spaces. Histological examination of the suture sites of all specimens was made. The preparations were stained with hematoxylin and eosin and impregnated according to the Gros-Bielschowsky technique for axis-cylinders.

The authors found that reconstitution of nerve sheath pathways may occur when well made unions of nerve ends are obtained by either the classic silk-epineurial or the plasma clot technique of nerve suture. However, in the case of the smaller nerves, the likelihood of reconstruction of these channels is greater when the plasma clot technique is used.

After the infliction of various grades of crush injuries on peripheral nerves, there remains or there is reestablished continuity of the nerve sheath pathways sufficient to permit the traversal by subperineurial injections of thorotrast.® The severer degrees of nerve compression do, at times, result in some obstruction of these neural pathways. There is a fair degree of correlation of the character of the suture site, the intensity of the scarring at the site of crush and the ease with which the radiopaque material traverses these zones.

ALPERS, Philadelphia.

GASTRIC MOTOR EFFECTS OF ACUTE REMOVAL OF CINGULATE GYRUS AND SECTION OF BRAIN STEM. B. P. BABKIN and W. C. KITE JR., J. Neurophysiol **13**:335 (Sept.) 1950.

Babkin and Kite found that bilateral ablation of the cingulate gyrus in acute experiments in dogs under chloralose-urethan anesthesia produced a moderate increase in the rate of contraction of the pyloric antrum. Intercolliculomesencephalic section of the brain stem increased the contraction rate of the pyloric antrum to a greater degree than did ablation of the cingulate gyrus. Hypothalamic ablation produced an increase in rate of contraction of the pyloric antrum, which was not further affected by section of the brain stem.

The authors present evidence that these effects were not due to traumatic stimulation.

ALPERS, Philadelphia.

ELECTROCORTICOGRAPHIC EFFECTS OF STIMULATION OF POSTERIOR ORBITAL, TEMPORAL AND CINGULATE AREAS OF MACACA MULATTA. M. A. LENNOX, R. H. DUNSMORE, J. A. EPSTEIN and K. H. PRIBRAM, J. Neurophysiol **13**:383 (Sept.) 1950.

Lennox and her colleagues found that unelicited spikes were recorded frequently from the periamygdaloid cortex, temporal pole and posterior orbital area, and simultaneously with needle electrodes in the region of the amygdala and hippocampus.

Electrical stimulation of the periamygdaloid cortex, temporal pole and posterior orbital and anterior cingulate areas produced similar electrocorticographic effects: (1) elimination of

strychnine spikes in areas other than that stimulated; (2) elimination of unelicited spikes in areas other than that stimulated; (3) production of an after-discharge locally, and sometimes in areas other than that stimulated. These effects were independent of one another, in that each might occur alone or in any combination with others.

Certain areal differences were noted. Stimulation of the anterior supracallosal area and of the temporal pole produced many of the effects. Stimulation of the periamygdaloid cortex produced a seizure discharge in all trials. Stimulation of the posterior orbital area eliminated strychnine and spontaneous spikes but did not result in a seizure discharge. No effect was produced by stimulation of the precallosal or subcallosal area. ALPERS, Philadelphia.

CHLORIDE LEVELS IN THE BLOOD OF ALCOHOLIC PATIENTS IN RELATION TO THE PHENOMENON OF CRAVING. W. D. SILKWORTH and M. TEXON, Quart. J. Stud. Alcohol **11**:381 (Sept.) 1950.

The craving phenomenon in the confirmed alcoholic may be the physiologic expression of a disturbed chemical equilibrium which potentiates and prolongs the spree. To test the possible relation of the chloride level in the blood to the craving phenomenon, 25 unselected patients were examined with special reference to their drinking habits, food habits, blood chloride levels and preference for salt.

The initial blood chloride levels (determined as sodium chloride) in 19 patients who expressed a craving for liquor averaged 345 mg. per 100 cc. These values were below the normal range of 435 to 500 mg. per 100 cc. in all cases. Coincident with the subsidence of the "craving" a rise toward more normal values oocurred. The average value after five days was 411 mg. per 100 cc., a rise of 19 per cent. The six patients who did not exhibit craving when admitted presented no significant deviations of the blood chloride level at that time or five days later.

Clinically, the perverted physiologic craving for liquor in prolonged alcoholic episodes is promptly corrected by increasing the salt intake in the diet or by the administration of isotonic sodium chloride solution parenterally. Within several minutes a dose of 2 Gm. of sodium chloride in 30 cc. of water, followed by a glass (200 cc.) of water, reduces the tremulousness, permits sleep and corrects the physiologic craving. ALPERS, Philadelphia.

Psychiatry and Psychopathology

ATABRINE [QUINACRINE] AND PSYCHOSIS. ANDRÉ FAVRÉ, Encephale **38**:381, 1949.

A white man aged 53 was treated in 1946 for intestinal parasites with quinacrine (atabrine®) hydrochloride 15 tablets 0.1 Gm. each, being given over three or four days and an additional 3 Gm. during another 12 days. Several days after the start of the medication a psychosis developed, manifested by manic agitation, mild confusion, grandiosity, flight of ideas and ideas of persecution. The patient distributed his money, wanted to go into various businesses and wrote innumerable letters. He was functioning so badly on his job that he had to be hospitalized. Abruptly, his manic episode changed to one of extreme depression, characterized by self accusations, introspection and cenesthopathy. He was treated successfully with electroshock, insulin coma and, finally, narcosis. This therapy was followed by complete recovery, which has been maintained without relapse for three years. There was no history of mental or nervous disease prior to 1946.

The authors review the literature of quinacrine psychoses. Hoops found one case in a series of 1,207; Udalagama, seven cases in 648; others have described similar cases. Vollmer and Liebig (1944) described two cases of quinacrine psychosis which were very similar to that reported by Favré. Their second patient also showed neurological damage in the form of fibrillations of facial muscles, aphonia, dysphasia and bulbar phenomena, paralysis of vocal cords and, finally, flaccid paralysis of the lower extremities. All the changes were reversible and were causally connected with the administration of quinacrine. Favré is firmly convinced that quinacrine produced the symptoms. He does not give the duration of the illness, merely stating it was abnormally long for quinacrine psychosis. Favré offers the opinion that the drug affects the diencephalic centers and in predisposed persons produces psychoses. The combination of quinacrine and pamaquine naphthoate U. S. P. XII (plasmochin®) does not seem to have any special tendency to produce a psychosis in predisposed persons. ZINKIN, New York.

THYROID FUNCTION IN MENTAL DISEASE: A MULTIPLE TEST SURVEY, K. M. BOWMAN, E. R. MILLER, M. E. DAILEY, A. SIMON and B. F. MAYER, J. Nerv. & Ment. Dis. **112**:404 (Nov.) 1950.

Serum protein-bound iodine, radioactive iodine, the basal metabolic rate and plasma cholesterol were determined as indexes of thyroid physiology in 26 schizophrenic patients, 16 patients with manic-depressive psychosis, 7 patients with mixed psychoses and psychoneurosis and 12 control patients. Serum protein-bound iodine values were lower than normal in the group with manic-depressive psychoses, in the low range of normal in catatonic patients and tended to be in the high range of normal in the patients with paranoid schizophrenia. The uptake of radioactive iodine by the thyroid was lower than normal in patients with manic-depressive psychoses and higher than normal in schizophrenic patients. The basal metabolic rate was lower in the schizophrenic and psychoneurotic group than in the controls. The variations in the values, although statistically significant and different from the controls, fall within the normal range. The psychoneurotic group is most nearly like the normal.

BERLIN, Chicago.

Meninges and Blood Vessels

PERCUTANEOUS CAROTID ANGIOGRAPHY: A TEAM TECHNIQUE, WITH A REPORT OF THE RESULTS IN SEVENTY CASES. M. WILKINSON, J. B. STANTON, D. P. JONES and J. M. K. SPALDING, J. Neurol., Neurosurg. & Psychiat. **12**:183 (Aug.) 1949.

Wilkinson and his associates describe a simplified technique of percutaneous carotid angiography in which a team of three, assisted by a nurse and radiographic technician, participated. Of a total of 70 angiograms, 66 showed good filling. This series comprised cases of intracranial tumor, epilepsy, hemangioma, disease of the cerebral arteries, intracranial aneurysm and other conditions not described. In 26 cases the angiogram was abnormal, being considered normal in the remaining 40. The highest percentage of pathologic changes appeared primarily in cases of intracranial tumor and hemangioma cerebri. Roentgenograms were presented in cases of a cerebral hemangioma, an aneurysm of the internal carotid artery and thrombosis of the middle cerebral artery, respectively. The first film, which represented the arteriogram, was taken two seconds after the injection was started, while further exposures at 3.25 and 4.5 seconds gave early and late phlebograms, respectively. Complications occurred in four cases: a local hematoma, lasting from three to seven days, in two cases; cervical sympathetic paralysis, lasting four weeks, in the third case, and an urticarial reaction on the face and neck, in the fourth case, in which there had been no conjunctival sensitivity to "uriodone" (a contrast medium). The authors indicate their preference for this technique because of its relative simplicity and infrequency of complications. They advocate intramuscular injection of paraldehyde prior to the procedure, rather than a general anesthetic.

N. MALAMUD, San Francisco.

Diseases of the Brain

BRAIN DAMAGE IN THE CHILD: A SEQUELA OF MATERNAL ISOIMMUNIZATION WITH THE B FACTOR. G. A. JERVIS, Am. J. Dis. Child. **79**:495 (March) 1950.

That incompatibility of the Rh factor between mother and child may result in brain damage in children who survive the acute phase of the disease in the neonatal period is a well established fact. The clinical picture of this sequela is essentially one of mental deficiency, choreoathetosis and extrapyramidal spasticity. Pathologically, there is evidence of brain damage, usually most pronounced in regions which are affected in kernicterus, i. e., the subthalamic nuclei and the lenticular bodies. More recently, the possibility has been considered that in the absence of Rh incompatibility, erythroblastosis fetalis, jaundice and kernicterus may result occasionally from maternal isoimmunization during pregnancy by the A or B factor.

Jervis describes the case of a girl who after birth showed erythroblastosis, icterus and generalized edema. On recovery from this acute episode, evidence of severe brain damage was present, consisting of idiocy, microcephaly, spastic tetraplegia and extrapyramidal manifestations. The mother's blood group was O; the child's group, B. The mother showed an abnormally

high anti-B titer. Both mother and child were Rh positive. The death of the patient occurred at the age of 6 years. The brunt of the pathologic changes was sustained by the white matter of the cerebral hemispheres. In addition, the cerebral cortex and the basal ganglia showed areas of cellular destruction. The author considers this case to be one of brain damage in the child due to maternal isoimmunization by the B factor.

ALPERS, Philadelphia.

NYSTAGMUS OF THE SOFT PALATE DUE TO TRAUMA. M. KLINGLER, Schweiz. Arch. Neurol. u. Psychiat. **64**:253, 1949.

A man aged 35 sustained a severe injury to his head. Examination a month later revealed pronounced nystagmus in all directions of gaze, Horner's syndrome and hemiataxia of the cerebellar type on the left side with hemianesthesia for pain and temperature on the right. A year after the accident, nystagmus was present only on upward gaze, and impairment of sensation for pain and temperature was limited to the ulnar portions of the right hand and forearm. On the occasion of the second examination, however, rhythmic myoclonic twitching involving both sides of the soft palate was observed. Similar rhythmic movements were also seen in the posterior wall of the pharynx and the left vocal cord.

In four cases collected from the literature palatal nystagmus was attributed to trauma, but in only two of these was the evidence for a traumatic origin of the condition particularly convincing. One of the two cases was similar to Klingler's case in that myoclonus of the right halves of the soft palate, pharynx and larynx was associated with hemiataxia on the same side and with hemianesthesia for pain and temperature on the left.

DANIELS, Denver.

Treatment, Neurosurgery

SUBACUTE COMBINED DEGENERATION OF THE CORD: I. RESPONSE TO LIVER EXTRACTS; II. TRIALS WITH VITAMIN B_{12}. C. C. UNGLEY, Brain **72**:382, 1949.

Ungley determined qualitatively the effects of treatment with liver extract in 44 patients with subacute combined degeneration of the cord. Changes were measured in both the individual signs and symptoms and the neurological condition as a whole. He used both crude and refined liver extracts in amounts needed to improve or arrest the neural lesions without reference to the effects on the blood picture. The weekly dose of liver extract was estimated to be hemopoietically equivalent to 40 micrograms of vitamin B_{12}; after six months of treatment, half this quantity was sufficient. He found significant improvement in 41 of the patients; the remaining three, who had been treated previously, showed no change. Ninety-five per cent of the improvement took place within the first six months of treatment. Relapses did not occur on a maintenance dose unless intercurrent infection supervened.

Eight patients were then treated with crystalline vitamin B_{12} in the same dosage. The improvement in these patients was studied and compared with the expected improvements based on treatment with liver extract; four of the eight patients exceeded the expected rate of improvement; two attained it, and two fell just short of it. The average reduction in the total score for neurological defect was 56 per cent, as compared with the expected 43 per cent. However, Ungley is of the opinion that pure vitamin B_{12} has no advantage over commercial liver extracts, particularly if their potency is determined clinically and microbiologically and expressed in terms of micrograms of vitamin B_{12}.

FRANKEL, Philadelphia.

A CLINICAL EVALUATION OF CERTAIN ANTIHISTAMINIC AND ANTISPASMODIC DRUGS IN PARKINSON'S DISEASE. A. S. EFFRON and P. G. DENKER, J. A. M. A. **144**:5 (Sept. 2) 1950.

Effron and Denker studied 80 unselected patients with Parkinson's disease (paralysis agitans). Most of the patients were in a fairly well advanced stage of the disease. The comparative effects of trihexyphenidyl (artane®), diphenhydramine (benadryl®) hydrochloride, methapyrilene (histadyl®) hydrochloride, scopolamine hydrobromide U. S. P., tripelennamine (pyribenzamine®) hydrochloride, phenindamine (thephorin®) tartrate, mephenesin (tolserol®) and combinations of some of these drugs were observed in treatment.

It was found that methapyrilene hydrochloride and mephenesin were the least effective. Tripelennamine hydrochloride and phenindamine tartrate helped about one third of the patients. Trihexyphenidyl, scopolamine hydrobromide and diphenhydramine hydrochloride were of value in approximately 70 per cent of the patients. Of the combinations used, tripelennamine hydrochloride and scopolamine hydrobromide resulted in improvement in about one half of the patients.

Best results were obtained with phenindamine tartrate and trihexyphenidyl. Good results were also obtained with phenindamine tartrate and scopolamine hydrobromide, and diphenhydramine hydrochloride and scopolamine hydrobromide. Eighty to ninety-five per cent of the patients derived benefit from these combinations.

ALPERS, Philadelphia.

THERAPY IN PSYCHOMOTOR EPILEPSY. F. M. FORSTER, J. A. M. A. **145**:211 (Jan. 27) 1951.

Psychomotor seizures are epileptic manifestations occurring alone or in combination with other types of seizures. The attacks are characterized by motor and/or psychic activity which is purposeful but irrelevant for the time and place, and the patient is amnesic afterward for the events that transpired during the seizure. There are no convulsive movements of tonic or clonic nature during psychomotor seizures.

Forster reviews a series of 87 patients who had psychomotor seizures either alone or in combination with other epileptic manifestations. Thirty-eight of these patients were studied prior to the advent of phenacemide (phenacetylcarbamide); only 25 of them, however, were followed for a sufficient time to permit evaluation. They had received the then available anticonvulsant preparations—diphenylhydantoin sodium, phenobarbital, mesantoin® (3-methyl-5-phenyl-5-ethyl-hydantoin) or trimethadione (tridione®). Employing these preparations, 17 patients showed decided improvement and 8 no improvement.

Of the 25 patients, six had psychomotor seizures only. Three of these were improved and three unimproved. Nineteen of the patients had both grand mal and psychomotor seizures. Fourteen of these were improved, and five were unimproved. The presence of multiple types of seizures would seem to be of favorable prognostic significance.

After the advent of phenacemide therapy, 49 patients were studied, but only 27 for a sufficiently long period to permit evaluation. Patients to be treated with phenacemide almost invariably were first given a trial with standard preparations, such as diphenylhydantoin sodium and phenobarbital. During these preliminary trials with diphenylhydantoin and phenobarbital, eight of the 27 patients became free from seizures, or nearly so.

Nineteen patients with psychomotor epilepsy were treated with phenacemide. The dose employed ranged from 1.5 to 3.5 Gm. a day. On this regimen, 13 patients became free from their psychomotor attacks; but four of the 13 patients manifested severe depressions, and phenacemide therapy had to be stopped. This left nine of the 19 patients with seizures well controlled on phenacemide therapy.

The patient with psychomotor seizures may thus be treated with diphenylhydantoin (dilantin®) sodium and/or phenobarbital, a therapy which has the advantages of simplicity and low toxicity, although establishment of control takes longer. Phenacemide is more specific against psychomotor seizures, and if the drug is efficacious the results are seen in a short time. However, in addition to the hematologic and hepatic damage seen with the use of other anticonvulsants, phenacemide has a disadvantage of its own—the development of depressions. Surgical therapy is available to those patients with distinct electroencephalographic foci, demonstrated on repeated testing, in whom medical therapy has failed.

ALPERS, Philadelphia.

EVALUATION OF A NEW AGENT (METHYL-ISO-OCTENYLAMINE) IN THE TREATMENT OF VASODILATING HEADACHES. G. A. PETERS and W. W. ZELLERS, Proc. Staff Meet., Mayo Clinic **24**:565 (Nov. 9) 1949.

Octin® (methylamino-iso-octene) was given intramuscularly and orally to patients with acute headaches of the migraine, histamine and tension types. Octin® hydrochloride (100 mg. per cubic centimeter) was given intramuscularly in doses of 0.5 to 1.0 cc., and the dose was repeated in 30 minutes if needed. Octin® mucate (2 grains; 0.13 Gm.) was given by mouth every 30 minutes until relief was obtained. Not more than 4 tablets were employed in the treatment of a single attack.

In the intramuscular series, 48 of 59 headaches were partially or completely relieved; in 11 instances no relief was recorded. Ten headaches recurred. No toxic reactions were recorded. Given orally, the drug relieved 15 of 26 headaches partially or completely, with no relief in 11 instances and no side reactions.

About 50 per cent of patients may expect complete relief from headaches when octin® is given intramuscularly. It is not effective in aborting acute attacks when given orally. The best results are obtained in migraine. The drug cannot be given intravenously, and it does not act as quickly as ergotamine. It is useful as an adjunctive form of treatment. It is of particular value in cases in which the patient may have abused ergotamine therapy and in cases in which the use of ergotamine may be contraindicated.

ALPERS, Philadelphia.

EFFECTS OF CORTISONE AND ACTH ON PERIARTERITIS NODOSA AND CRANIAL ARTERITIS: PRELIMINARY REPORT. R. M. SHICK, A. H. BAGGENSTOSS and H. F. POLLEY, Proc. Staff Meet., Mayo Clin. **25**:135 (March 15) 1950.

Cortisone was given to three patients with periarteritis nodosa (essential polyangiitis) and two with cranial arteritis; two other patients with periarteritis nodosa received pituitary adrenocorticotropic hormone (ACTH). The diagnoses were confirmed histologically. Treatment was continuous or intermittent from three weeks to four and one-half months.

All seven patients had prompt subjective relief. Fever subsided in 24 to 72 hours, and sedimentation rates decreased to normal more gradually. Partial relapses occurred in five patients on withdrawal of the drug, followed by improvement when treatment was resumed.

The three patients with periarteritis nodosa were critically ill when cortisone therapy was begun. Despite initial improvement, two died in cardiac and renal failure; the other has severe and progressive hypertension. Necropsy showed complete healing of all arterial lesions. In the process of healing, fibrous obliteration of the lumens of the vessels had occurred, causing widespread visceral infarction.

Evidence of hypercorticalism developed in most patients during treatment.

ALPERS, Philadelphia.

TREATMENT OF MIGRAINE WITH DRAMAMINE. E. BRENTAN, Rocky Mountain M. J. **47**:197 (Feb.) 1950.

Brentan found dimenhydrinate ("dramamine") effective in seven cases of migraine. When the drug was used at the onset of prodromal symptoms, all the manifestations of the migrainous headache were aborted, and the patient was able to resume normal activities almost immediately. All these patients had been treated previously with the usual medicaments and had received only slight, if any, relief.

J. A. M. A.

ARTANE IN THE TREATMENT OF PARKINSONISM. BASIL K. ELLENBOGEN, Lancet **1**:1034 (June 3) 1950.

The author treated 12 Parkinsonian patients with artane® (trihexyphenidyl) for three to six weeks and reports his preliminary observations. In seven of the patients the disease was of the postencephalitic type; in two, of the senile type, in two it was idiopathic, and in one it was post-traumatic. The initial dose of trihexyphenidyl was 2.5 mg., the daily dose being increased by this amount to a total of 12.5 mg., in five doses. When this amount was exceeded, no greater improvement was obtained, and side reactions developed, including headache, giddiness, slight cycloplegia and dryness of the mouth.

The author found that trihexyphenidyl is a powerful remedy, possessing the advantages of the belladonna alkaloids without their disadvantages. Removal of inertia, relaxation of spasm and reduction in tremor are achieved, but not at the expense of dryness of the mouth and paralysis of accommodation. Nor is it necessary to increase the dose to the limit of tolerance to achieve the greatest benefit. Where trihexyphenidyl is effective, it becomes so immediately and dramatically. Where there is much rigidity, its relaxation may reveal a latent tremor or tremor may be aggravated. Use of the drug was more successful in the post-encephalitic group than in the senile and idiopathic groups.

MADOW, Philadelphia.

NEUROSURGICAL TREATMENT OF PERSISTENT PAIN. J. C. WHITE, Lancet **2**:161 (July 29) 1950.

White reviews his experience and that of his associates in 1,100 operations performed for the relief of otherwise intractable pain of one form or another. He describes in this paper the three operations which have interested them most—chordotomy, sympathectomy and prefrontal leucotomy—and discusses their relative merits and demerits.

Chordotomy is so slight a risk as compared with the psychic damage of leucotomy that White and his colleagues favor its trial, on one side at least, if there is any reasonable chance of success. Their results with chordotomy in cases of malignant and nonmalignant disease show that relief of pain was satisfactory in 73 to 88 per cent of the cases of abdominal and pelvic tumors but was less complete in cases of tumors of the breast, lungs and bones, in which high spinal and thoracic metastases are common. The relief in 71 per cent of cases of amputation stump neuralgias and painful conditions associated with disease of the spinal roots is comparable to that seen in the more favorable varieties of malignant disease. After a unilateral chordotomy the patient may begin to complain of discomfort on the opposite side. Since a bilateral operation is often unnecessary, and because they have found that urinary complications are much less frequent if both anterior quadrants are not transected at a single stage, White and his colleagues prefer to start with a conservative unilateral chordotomy unless pain is severe on both sides. A second incision on the opposite side can be done later.

The spinothalamic tract was divided in the medulla oblongata in a number of cases to relieve neuralgia of the shoulder, neck and pectoral region.

White emphasizes that the effectiveness of sympathectomy is limited to pain originating in the heart, aorta and abdominal viscera. It will not relieve pain originating in the esophagus, bladder, prostate or cervix uteri, to which the majority of afferent fibers run in the vagus or sacral nerves. Also, sympathectomy cannot be expected to relieve pain in malignant disease of the viscera, since this does not usually develop until the lesion has burst through the capsule of the organ and invaded structures in the parietal pleura or peritoneum, which are supplied by spinal nerves.

In addition to its importance in the control of visceral pain, sympathectomy is of great value in the relief of causalgia and the post-traumatic dystrophies. In these conditions the beneficial result seems to be related to improvement in circulation. It is doubtful whether any pain pathways are interrupted.

In view of the psychic deterioration which ensues when the frontothalamic connections are cut on both sides, White feels that there is no justification for recommending this operation for the relief of conditions that can be taken care of by an adequate chordotomy, rhizotomy or sympathectomy. It should be undertaken only when other measures are already known to be ineffective or after they have been tried without success.

After bilateral prefrontal leucotomy for pain patients have been more upset psychically than those operated on for schizophrenia or other psychiatric conditions. As there is no contraindication to the carrying out of a frontal leucotomy in stages, White and his colleagues favor unilateral complete transection of the frontal white matter in all cases in which the operation is done for relief of pain. If pain returns or is inadequately relieved, a second section on the opposite side can be carried out later. In these circumstances pain is relieved as effectively and with less psychic deterioration than after the one-stage bilateral operation.

ALPERS, Philadelphia.

"MEDICAL SYMPATHECTOMY" IN HYPERTENSION: A CLINICAL STUDY OF METHONIUM COMPOUNDS. R. TURNER, Lancet **2**:353 (Sept. 2) 1950.

Since the hexamethonium and pentamethonium compounds block the transmission of nerve impulses through autonomic ganglia, their potential range of usefulness is wide. This preliminary paper is concerned with their possible use in patients with essential hypertension in order to produce effects comparable to those of surgical sympathectomy.

Turner reports three illustrative case histories and the results of treatment with these drugs. He concludes that the methonium drugs have as yet no place in the routine management of hypertensive patients, though they may prove useful in the treatment of resistant symptoms related to hypertension.

There is no evidence as yet that continuous reduction of blood pressure by drugs which paralyze the autonomic ganglia will prove beneficial to hypertensive patients in the long run, and it may well prove harmful to some of them. Possibly a study of the methonium compounds will throw light on the etiology of essential hypertension.

ALPERS, Philadelphia.

PENTAMETHONIUM IN HYPERTENSION. S. SAVILLE, Lancet **2**:358 (Sept. 2) 1950.

The customary treatment for "essential" hypertension has been rest in bed, sedation and regular venesection, but many patients have failed to respond significantly or to maintain the initial improvement. Some of those with serious symptoms who were not responding satisfactorily to these measures were treated with pentamethylene bistrimethylammonium, otherwise called pentamethonium, in the form of its bromide or iodine salts.

The results in five cases suggest that pentamethonium bromide may be useful in the treatment of at least some forms of hypertension. In all these cases it has relieved troublesome symptoms and has apparently arrested the progress of the disorder. The principal side effect to be watched for is postural hypotension.

ALPERS, Philadelphia.

CONSERVATIVE TREATMENT OF TRIGEMINAL NEURALGIA. J. SOLÉ SAGARRA and L. ALONSO DE OLARTE, Am. med., Barcelona **25**:373 (Nov.) 1949.

Solé Sagarra and Alonso de Olarte direct attention to the causal role of irritation of the gingival end branches of the trigeminus on the development of trigeminal neuralgia and onset of the crises. The authors cite observations on a large number of patients of each sex between the ages of 36 and 82 in whom neuralgia had lasted for five to 15 years. Thiamine hydrochloride, roentgen radiation, nicotinic acid, bee venom and histamine iontophoresis failed to relieve their symptoms. The point of maximal pain in the majority of the cases was on either the upper or the lower gum. The differentiation from other types of neuralgia was made by the following characteristics of pain: (1) The sensitivity of the whole trigeminal territory is intact; (2) the bouts of pain are intermittent; (3) pain is not associated with pain from other nerves. Successful treatment consisted in infiltration of the gums with a 20 per cent phenol solution in glycerin, which was injected at the point of maximal pain on either the upper or the lower gum or both. Neuralgia was controlled by the first infiltration in all cases. In three of six cases neuralgia recurred one or two years after infiltration. The pain was milder than it was before the treatment. It was controlled by a second infiltration, which was given at the same point. In two cases permanent cure was obtained from one infiltration without recurrence, two and five years, respectively, after treatment.

J. A. M. A.

RESULTS OF EIGHTEEN MONTHS OF STREPTOMYCIN THERAPY OF TUBERCULOUS MENINGITIS IN CHILDREN. J. CHAPTAL, D. BRUNEL, PIETRI and OTHERS, Arch. franç. pédiat. **6**:561, 1949.

Chaptal and co-workers gave streptomycin therapy to 50 children with tuberculous meningitis during the period of January 1948 to June 1949. Of 26 children who died during the treatment, only 24 were considered therapeutic failures, since two died within 36 hours after admission to the hospital. At present, 19 (44 per cent) are considered cured. One to 2 Gm. of the drug, depending on the age of the child, was administered daily by the intramuscular route until clinical and biologic recovery was maintained for two months after the cerebrospinal fluid had been restored to normal. Poor results were obtained with the administration of streptomycin by the intramuscular route alone. Additional administration of the drug by the intraspinal route is indispensable. A 10 to 20 day course with 0.01 to 0.05 Gm., depending on the age of the child, in two divided doses daily is recommended and may be repeated if the albumin content of the cerebrospinal fluid increases or shows a tendency to stabilization at a pathologic level. Spinal puncture should be performed daily during the treatment by the intraspinal route, and later every eight or 15 days or at least once a month. Eleven of the 26 patients who died were less than 2 years of age; 8 were between 2 and 6, and 7 were between 6 and 15. Treatment was begun after the tenth day of the disease with 18 of the 24 therapeutic failures. Twelve of these patients were in coma on admission; 5 had bulbar disturbances, and 15 presented a paralytic

syndrome. Intracranial hypertension resulting from acute hydrocephalus occurred during the initial stages of treatment, as well as between the fifth and eighth month, and was associated frequently with cerebrospinal block. Intracranial hypertension was the cause of death in 16 patients. Neurosurgical treatment should therefore be frequently combined with medical treatment. Three of the 19 patients who recovered were less than 2 years of age when treatment was instituted; 4 were between 2 and 5 years; 4 were 6 years of age; 4 were between the ages of 7 and 10, and 4 between the ages of 10 and 15. Treatment was instituted before or at the tenth day in 11 of the 19 patients who recovered. Duration of the treatment of these patients varied from 10½ to 23 months, and one to 12 months have passed since treatment was discontinued. Deafness resulted in four patients.

J. A. M. A.

CUTTING OF THALAMOFRONTAL TRACTS IN UNCONTROLLABLE PAIN. V. T. RIECHERT, Med. Klin. **44**:689 (June 3) 1949.

The cutting of thalamofrontal tracts for intractable pain has been recently suggested by Freeman and Watts. Riechert so far has employed the procedure in six patients. The operation is of value also in types of pain which could not be influenced by surgical measures formerly in use for the control of pain. The author treated successfully one patient with anesthesia dolorosa and two patients with intractable pain from advanced syringomyelia. The type of pain presented by the patient with anesthesia dolorosa is seen frequently after electrocoagulation of the gasserian ganglion. Pain which was formerly piercing and intermittent often becomes burning, continuous and less bearable. To reduce to a minimum the undesirable effects of the cutting of the thalamofrontal tracts, the author performs the operation with the use of local anesthesia and, if possible, during an attack of pain. The patient is urged to describe the effect of the operative procedure on the pain. In a patient with syringomyelia the pains were localized in the neck, shoulders and upper part of the arms. The tracts were severed first on the right side, and the patient stated that the pains on the left side disappeared, whereas on the right side they became more intense and extensive, involving also the hand. Section of the tracts on the left side gradually reduced the area of pain, which finally disappeared. On the basis of exploratory operations performed with the use of local anesthesia, the author has gained the impression that the cutting of a comparatively small portion of the thalamofrontal tracts, chiefly those leading to the median basal orbital part of the brain, is most effective. He also observed that patients who before the operation had been addicted to drugs did not manifest withdrawal symptoms when use of the drugs was stopped after the operation. The time elapsed since operation is too short to enable the author to state whether the pain has been permanently abolished or may return.

J. A. M. A.

Encephalography, Ventriculography and Roentgenography

HYDATID DISEASE OF VERTEBRAE. L. J. WOODLAND, M. J. Australia **2**:904 (Dec. 24) 1949.

The frequency of hydatid disease of bone has been estimated at between 0.59 and 2.24 per cent. The common sites affected are the vertebrae, the pelvis, the femur and the humerus. The vertebrae are the most frequently affected bones, representing 50 per cent of the cases. The spongy tissue of the vertebral bodies is a favorite site when hydatid disease attacks a bone. The infection, as with hydatid disease elsewhere, usually starts in childhood. While it is confined to the bone, the growth of the hydatid is so slow that symptoms do not become evident before adult life. In the cases reviewed the average age at which symptoms occurred was 34 years. There are no symptoms until the destruction of the bone leads to fracture or dislocation or until the hydatid cyst has erupted from the bone and caused pressure or swelling. In four of the five cases reviewed by Woodland there were symptoms of pressure on the spinal cord. Four of the patients died, the average duration of life after the onset of symptoms being 11 years. The original site of infection in three cases was the upper lumbar vertebra and in two cases the midthoracic vertebra. The diagnosis of vertebral hydatid disease is difficult. The general condition is usually excellent. Symptoms are due to fracture or subluxation of the affected vertebra or to pressure by extraosseous extensions, which may be confused with lipoma

or cold abscess. Although vertebral hydatid disease has no pathognomonic roentgenologic signs, certain features, such as absence of periosteal reaction, minimal collapse, slight involvement of intervertebral spaces only and increased density of bone, together with areas of destruction and involvement of contiguous ribs when a thoracic vertebra is affected, aid in the diagnosis.

J. A. M. A.

Diseases of the Skull and Vertebrae

METABOLIC CRANIOPATHY: A REVIEW OF THE LITERATURE WITH REPORT OF A CASE WITH DIABETES INSIPIDUS. S. DANN, Ann. Int. Med. **34**:163 (Jan.) 1951.

There is much suggestive clinical and experimental evidence that metabolic craniopathy is a clinical entity, probably endocrine, and possibly pituitary, in origin.

The condition is suggested when a middle-aged or elderly woman complains of obesity, persistent cephalalgia and hirsutism. If, in addition, she is hypertensive and complains of muscular weakness and menstrual disturbances, the clinical impression is strengthened. If, further, there are a variety of mental and neurologic disturbances pointing in general to interference with the higher mental functions and focal disease of the cranial nerves in the absence of a specific etiologic agent, these may be considered as secondary supporting features. The presence of roentgenologic changes in the skull is an added, but not essential, sign.

Dann describes a case of metabolic craniopathy complicated by diabetes insipidus in a woman of 28. Polyuria was brought under control with vasopression injection U. S. P. (pitressin®), but the headaches were unrelieved by various forms of medication. When the case was restudied almost a year later, the patient was despondent to the point of threatening suicide because of the headaches. Aminoacetic acid, taken for only a two week period, did not help the headaches. The patient had a fixed idea that pregnancy might ameliorate her condition and finally conceived a year later. The pregnancy ended in miscarriage of a macerated fetus at three months.

During pregnancy a dose of vasopressintannate injection U. S. P. controlled polyuria for three to seven days; since the abortion a daily injection has been needed. Headaches are now uncommon and are brought on by excitement. Her weight has increased about 30 pounds (13.6 Kg.) since onset of her illness. There is no hirsutism, but she has slight acne and an acromegaloid appearance. Roentgenograms of the skull show generalized thickening of the inner table of the calvarium "suggestive of metabolic craniopathy." The patient remains intelligent, is well oriented and can carry on her household duties.

Treatment of metabolic craniopathy is unsatisfactory. Aminoacetic acid in large doses should be tried, and possibly radiation therapy should be attempted more frequently. Much more clinical and laboratory investigation is necessary before this syndrome can be placed on a firm basis diagnostically and therapeutically.

ALPERS, Philadelphia.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

S. Bernard Wortis, M.D., Chairman, Section of Neurology and Psychiatry of the Academy, Presiding
Combined Meeting, Feb. 14, 1950

Septic Meningitis with Bacitracin Therapy: A Further Report. DR. PAUL TENG.

During the past two years 13 patients with purulent meningitis have been treated with bacitracin. The following organisms were found: Staphylococcus, in 6; Streptococcus, in 2; Pneumococcus, in 1; mixed organisms, in 2, and an unidentified gram-positive coccus, in 2.

The causative organisms found to be resistant to penicillin and/or other antibiotics in 10 patients were proved to be so either by laboratory or by clinical observations.

Eight patients were treated with bacitracin by the intrathecal or by the intraventricular route, or by both routes whenever this was indicated. This method was supplemented by the intramuscular injection of bacitracin and other antibiotics when that seemed advisable. In every instance the causal organism was found to be resistant to penicillin, which, in fact, had been previously used in excessive amounts both by subarachnoid and by intramuscular injections, yet without avail. After bacitracin therapy six patients recovered. Five patients were treated primarily with bacitracin by intracranial and subarachnoid administration, supplemented with systemic use of penicillin and bacitracin, and three recovered. Thus, in a small series of 13 patients with purulent meningitis receiving this combined antibiotic therapy, nine recovered, a survival rate of approximately 70 per cent. Among the surviving patients, the youngest was 6 weeks and the oldest 76 years of age.

Of the four patients who died, 1 had an inoperable tumor in the pineal region, which caused complete block of the ventricular system and meningitis; 1, thrombosis of the middle cerebral artery with extensive cerebral infarction and infection of the brain tissues; 1, multiple brain abscess and long-standing extensive purulent encephalitis, and 1, an undisclosed brain abscess, meningitis, extensive bronchopneumonia and cardiac failure.

Bacitracin, an antibiotic produced by the Tracy I strain of Bacillus subtilis, can be administered directly to the central nervous system with safety. This has been proved by my experiments in laboratory animals and in 50 consecutive cases of neurosurgical infections.

DISCUSSION

DR. SIDNEY W. GROSS: I have had the opportunity of seeing some of the patients treated by Dr. Teng. The striking response to bacitracin after failure of other antibiotics was best demonstrated in an infant with a subdural infection which failed to respond to penicillin but cleared up promptly with bacitracin. Dr. Teng has told of the advantages of bacitracin in the treatment of infections of the central nervous system. The following deserve reiteration. Many bacterial strains resistant to penicillin are sensitive to bacitracin. Bacitracin is relatively nontoxic when used by direct application to the subdural or subarachnoid spaces or directly to the brain. Individual sensitivity to bacitracin has not yet occurred in any patient.

DR. J. LAWRENCE POOL: I should like to open this discussion by congratulating Dr. Frank Meleney on the discovery and development of bacitracin. Next, I should like to congratulate Dr. Paul Teng. I have had the pleasure of his assistance in cranial surgery for psychoses, during which bacitracin was frequently used as a precautionary measure and once or twice, at a state hospital, to combat wound infections, caused by these psychotic patients clawing at their scalps. In every case bacitracin proved effective, and at no time have we noted any ill effects, such as neurological changes or convulsive seizures, from its use.

Bacitracin has also been used with great success when other antibiotics failed (at the Neurological Institute of New York), again without ill effects. I feel, therefore, that for certain conditions it has already proved more effective and less hazardous when applied to the brain than is penicillin or streptomycin.

In a word, bacitracin is apparently here to stay and, more than this, may be counted on as an antibiotic agent that will often prove efficacious when other antibiotics are no longer effective.

Dr. Frank L. Meleney: I am very happy to have the opportunity of discussing this paper of Dr. Teng's, not only because of its intrinsic worth but because it clearly demonstrates the intellectual curiosity and determination of the author himself.

A little over a year ago Dr. Teng was sent over from China to work under my direction in our laboratory for bacteriological research in the department of surgery. He was sent over by a former student of mine, now dean of the Shantung Christian University Medical School, who stated that Dr. Teng was the most promising surgeon who had ever graduated from that institution in his experience.

In spite of the handicap of language, Dr. Teng pursued his studies in the field of antibiotics with great avidity, and, because of his interest in neurosurgery, he undertook to study the effects of bacitracin on the nervous system, both normal and pathological. His first experiments were carried out with dogs and cats, and when these results seemed to indicate that bacitracin was of low toxicity when applied to the meninges, the surface of the brain or the ventricles, it was applied cautiously in the treatment of neurological infections in man.

I believe that his report brings clear proof that bacitracin is able to bring infections of the central nervous system under control, even when administered late in the course of the infection, and after the condition has failed to respond to other methods of treatment. He has also demonstrated that its application to the surface of the brain, to the ventricles, and even to brain tissue, in therapeutic concentrations is without any evidence of toxicity.

It would seem, therefore, that bacitracin is at present the drug of choice in the treatment of neurological infections.

Theoretical and Practical Observations on Patients Subjected to Topectomy. Dr. Paul H. Hoch, Dr. James P. Cattell, Dr. Harry H. Pennes and Dr. Gilbert H. Glaser.

Fifty-five patients who underwent topectomy were reported on. Sixteen, or 29 per cent of the 55 patients, can be paroled. Of the 55 patients, 47 had chronic schizophrenia, of whom 9 were paroleable, and 8 had pseudoneurotic schizophrenia with no deterioration, of whom 7 were paroleable. Twelve per cent of the patients preeminently belonging in the nondeteriorated group show a good clinical improvement, whereas the others are considered "administratively" improved. These patients also show a palliative, and not a curative, improvement.

Attention was called to the difference in these two forms of improvement, indicating that in deteriorated schizophrenic patients the results are far less good than in nondeteriorated schizophrenic patients and in patients with chronic obsessive and phobic neuroses. Prognostic tests with amobarbital (amytal®) sodium were also described.

Topectomy is probably as effective as lobotomy in improving the patient's mental condition, but, apparently being a small operation, it is less damaging. Side effects of brain damage are not seen as often or as strikingly in topectomy as in lobotomy.

The operative material was divided into two groups. In one group the upper quadrant of the frontal lobe was operated on, and in the other half, the lower. There were no significant differences in therapeutic outcome between the two forms of operation.

Some theoretical aspects of topectomy were then discussed in relation to cerebral function and psychodynamics.

DISCUSSION

Dr. J. Lawrence Pool: I have never done topectomy for relief of major psychoses and allied mental disorders without the recommendation of at least one competent psychiatrist. The operation was designed as a more specific surgical procedure than prefrontal lobotomy, for it was felt that the visualization of the frontal lobes, which is necessary in the topectomy procedure, provided a better opportunity for estimating the region in which the operation was to be done and the extent of the operation. We have found it impossible to carry out any cortical removals according to Brodmann's areas. We can only estimate the excision of this area in a very crude way. Furthermore, it has been possible to arrive at some quantitative estimate of each operation by measuring and weighing the amount of cortex removed.

The amount of cortex removed, however, often seems an important factor. For the major psychoses approximately 30 to 35 Gm. of cortex must be removed from each frontal lobe if improvement is to occur and be of lasting value. Less than this amount is often sufficient for the relief of intractable pain or the simpler depressions not responding to psychotherapy or shock therapy. As a rule, removal of more than 35 Gm. from each side does not help the schizophrenic patient if the removal of 35 Gm. has not already helped. (The amount of cortex removed in topectomy, incidentally, is roughly only about 50 per cent of the amount of cortex sacrificed by isolation in a "standard" prefrontal lobotomy. Thus, topectomy is actually a less radical procedure, although the operation itself may require more time. The average duration now, provided no associated studies are carried out, is two hours and 15 minutes, and the operation can be carried out through 2 inch [5 cm.] trephine openings or with a single bifrontal bone flap.)

There has been a 12 per cent incidence of postoperative seizures, including cases in which only one or two seizures have occurred in the immediate postoperative period. All patients who had postoperative seizures have had no further convulsive episodes, provided they faithfully took anticonvulsant medicaments in adequate amounts.

Topectomy has made possible incidental studies on the cingulate gyri, the orbital surface of the frontal lobes and the anterior aspect of the temporal lobes, stimulation of these areas having regularly produced transitory autonomic effects, which will be reported later.

In conclusion, it is of interest to note that there has not been a single operative fatality following any topectomy carried out anterior to the coronal suture line in the series of nearly 200 consecutive cases.

Itch Sensation in the Skin: Experimental Observations on the Neural Mechanisms Involved. Dr. David T. Graham, Miss Helen Goodell and Dr. Harold G. Wolff.

Itching was elicited by the application of cowage (Mucuna pruriens) to the skin. The sensation which it produced was indistinguishable from that which follows the bite of a mosquito. It was found that the sensation of itching could be analyzed into two components, as follows:

Procaine was infiltrated about a cutaneous nerve, after which there developed distal to the site of infiltration areas in which pinprick elicited only a sharp, superficial, well localized pain of short latency—the "first" pain. The slower, diffuse, burning "second" pain was not perceived. In such areas cowage elicited a sharp, pricking, superficial and readily localized itch. This is one component of the itch sensation. After maintaining a sphygmomanometer cuff around the upper arm at a pressure of 200 mm. mercury for 20 to 30 minutes, pricking pain could no longer be elicited in the distal part of the extremity, where pinpoint elicited pain of long latency, poorly localized and of aching or burning character—the "second" pain. Light touch sensibility was also absent. Cowage applied to these areas still elicited itching, but the itching was diffuse, poorly localized, seemed to be a little distance beneath the surface of the skin and was best described as "burning." Similarly, when a cutaneous nerve was anesthetized by cold, no pricking component, but only the diffuse burning component of itch, was elicited distal to the application of the cold in the zone of distribution of the nerve. Itching never occurred in the absence of both types of pain sensitivity, although it did occur in the absence of touch sensitivity.

We therefore conclude that the sensation of pricking itch is mediated by the large fibers which subserve the "first" pain, and the burning itch, by the small fibers responsible for the "second" pain.

In healthy human subjects pain thresholds in the skin were ascertained by the thermal radiation method of Hardy, Wolff and Goodell before, and intervals after, the administration of vasodilating agents. The pain threshold was lowered during cutaneous vasodilatation, and these subjects also reported spontaneous itching.

DISCUSSION

Dr. Marion B. Sulzberger: These studies on itching by Graham, Goodell and Wolff should be welcome indeed to all clinicians, particularly to dermatologists, for it is likely that itching causes as much trouble as does pain.

In my experience, it is by no means only vasodilation which leads to increased susceptibility to itching: Cooling, as by fanning; heating, as by the bedclothes; changes of pressure, as by removal of constricting clothing; moving the piloerector structures, as by stroking or tickling;

interference with and blockage of the pouring out of sweat, and many other chemical and physical agencies acting on the skin will, in given circumstances, cause itching. It is therefore my opinion that the interesting concept of the role of vascular dilatation in producing itching will be found to apply only to particular forms of pruritus and to particular states of itch susceptibility.

PHILADELPHIA NEUROLOGICAL SOCIETY

Helena E. Riggs, M.D., *Presiding*

Regular Meeting, Nov. 3, 1950

Syphilis of the Central Nervous System Associated with Presenile Changes: A Neuropathological Study. Dr. Thomas C. Parsons (by invitation).

The case presented was considered of interest in that it illustrated the difficulties in diagnosis of dementias occurring in middle age. A white woman aged 49 gave a history of an insidiously developing organic psychosis with generalized convulsions and presented signs suggestive of Parkinsonism. Reactions of both the blood and the spinal fluid were negative for syphilis. The histopathological picture fulfilled the criteria for dementia paralytica, but senile plaques were also present.

The differential diagnosis in this case rested between presenile dementia with dementia paralytica and a presenile dementia complicated by meningeal syphilis.

Similar cases in the literature reported by Bonfiglio, Kreutzfeld, and Lowenberg and Rothschild were cited, and, on the basis of Alzheimer's and Struwe's observations of the presence of senile plaques in cases of syphilis of the central nervous system, it was suggested that the Alzheimer disease entity might be released by syphilitic involvement of the central nervous system, as well as by the variety of other etiological factors suggested by Malamud and Lowenberg.

As seen in this case, pathological studies may not only fail to resolve a diagnostic problem but may actually increase its complexity.

DISCUSSION

Dr. Helena Riggs: This case interested me very much, because the number of cases in which syphilis of the central nervous system is accompanied with a negative Wassermann reaction is very limited. Recently Dr. Wilson, Dr. Rupp and I reviewed our cases of syphilis at the Philadelphia General Hospital, from the point of view both of the serologic reactions and of the neuropathologic changes. In our series of some 300 cases there were none in which the diagnosis of dementia paralytica histologically was made and the serologic reactions for syphilis were negative.

Dr. George D. Gammon: How long after treatment did the patient die?

Since the advent of penicillin therapy for syphilis, the few pathological reports which have appeared tend to agree that the outstanding feature in cases of death more than three or four months after therapy is a considerable dissolution of inflammatory exudates. In some instances it has been difficult to identify the process as syphilitic unless the specific changes, e. g., the lesions of the tabes or the derangement of cortical architecture of dementia paralytica, were present. In this case the picture was the reverse, since inflammatory exudate remained despite penicillin therapy.

Dr. Matthew T. Moore: I should like to ask Dr. Parsons whether he used the Jaenel stain, a specific stain for the rod cells and the stains of Alzheimer for neurofibrils. I did not see preparations with the Alzheimer stains on the screen.

Dr. Thomas C. Parsons (by invitation): In answer to Dr. Gammon's question: This patient was not suspected of having had syphilis of the central nervous system or any form of syphilis, for the serologic reactions were consistently negative. Penicillin was given because she exhibited signs of meningeal irritation about a week prior to her death.

The Dublin stain and the Bielschowsky stain were used.

Dr. Helene Riggs: May I answer Dr. Moore? We felt we were capable of recognizing rod cells without special stains. As to the silver stains, the Dublin stain, the Wilder stain and several of the Bielschowsky modifications were used.

The Parkinsonian Syndrome and Brain Tumor: Report of a Case. Dr. Francis C. Grant.

A man aged 42 exhibited the symptoms of Parkinsonism with spasticity in the left extremities after an illness with encephalitis at the age of 13 years. At the age of 30 he had sustained a blow on the top of the head just to the right of the midline, roughly in the parietal region. This neither increased nor decreased the spasticity on the left side, but it did increase the severity of his headaches at the age of 35. He became nervous and irritable, and it was difficult for him to work. At the age of 40 the headaches became so severe that he had to stop work entirely.

The case is presented for three reasons:

1. When the patient was first seen, there did not seem to be much question as to what his lesion was. When I first saw him, he presented the usual picture of parkinsonism, and I wondered why he had been sent to a neurosurgical clinic.

2. After air studies, we were convinced that he had a large cyst with a nubbin of tumor. The cyst contained yellow fluid, which promptly coagulated on removal. The adjacent tumor, instead of being the expected astrocytoma, was a meningioma springing from the falx. I cannot remember seeing a cyst containing fluid with a high protein content that coagulated promptly in connection with a meningioma.

3. His tumor lay well back in the parietal region, whereas the cyst lay near the motor cortex. Apparently, the cyst produced his symptoms, because on the most careful neurological study we could find no sensory loss of any kind. He certainly had none of the striking parietal lobe symptoms that we should have expected from a lesion in this region.

The tumor on removal weighed 61 Gm. and measured 6 by 5 by 4 cm. Pathologically, it poved to be a meningioma, type II, variation 2.

Dr. Rudolph Jaeger (by invitation): I should like to ask Dr. Grant whether he performed a ventriculographic or an encephalographic study in this case.

Dr. Francis C. Grant: A ventriculographic study.

Dr. Rudolph Jaeger: Did you enter the ventricle on the side of the cyst?

Dr. Francis C. Grant: No, I struck the cyst. I did not encounter the ventricle on that side.

Dr. Rudolh Jaeger: Did you inject air on one side only, or on both sides?

Dr. Francis C. Grant: I injected air on both sides. I think that when one hits a cyst and removes yellow fluid, one had better introduce some air into the cavity.

Dr. Rudolph Jaeger: Then you went to the other side and got clear fluid?

Dr. Francis C. Grant: Yes, there was no connection, apparently, between the cyst and the left lateral ventricle.

Dr. Rudolph Jaeger: I do not recall having seen a person with a long-standing brain tumor, similar to this man's, who exhibited such typical signs of Parkinson's disease. The expressionless face and spastic extremities, with a pill-rolling tremor, are seldom combined with brain tumor to give this picture. It is possible that this man may have had both a brain tumor and Parkinson's disease.

Cysts associated with meningiomas form between the brain and the tumor and usually contain clear fluid. The presence of straw-colored fluid in this case is unusual.

Dr. Robert A. Groff: I have not encountered a meningioma with associated cyst that I can remember, or at least one that, according to the ventriculogram, looked like an intracerebral cyst. I have, of course, seen astromytomas with cysts, and I have tapped them, in an attempt to obtain a ventriculogram, and found that the tumor was an astrocytoma. Dr. Grant, did you excise the cortex to reach the cyst cavity?

Dr. Francis C. Grant: Yes.

Dr. Robert A. Groff: And then you found that it was a circumscribed lesion arising from the falx?

Dr. Francis C. Grant: I cut into the cyst, and in the posterior wall of the cyst was the tumor. I expected it to be soft, but it was not; it was solid, and the brain could be brushed away

from it. I suddenly realized that I was up against a meningioma. It was a complete surprise to me.

Dr. Joseph Yaskin: On July 31, 1949 a woman aged 35 was admitted with a Parkinsonian syndrome on the left side and a history of encephalitis years previously. Were it not that she complained of severe headache and had an occasional Jacksonian fit involving the left side, we should have missed the diagnosis completely. Indeed, I did not take it very seriously; but, because of the urging of the residents, an air study was done, and operation revealed a spongioblastoma.

As to the formation of the cyst, we must assume that a meningioma began to grow from the meninges, and during the invasion of the brain by the tumor something happened to cause the formation of fluid. Was that your idea, Dr. Groff?

Dr. Robert A. Groff: Yes.

Dr. Joseph Yaskin: Just what the mechanism is, I do not know. As a matter of fact, most meningiomas do not penetrate the surface of the brain; they compress it. This tumor was really in the depths of the subcortical tissue?

Dr. Francis C. Grant: Yes.

Dr. Joseph Yaskin: The invasion of the brain and the subcortical region by the tumor might be the determining factor in the formation of the fluid.

Dr. Samuel Zeritsky: I am puzzled by the exhibition of the visual field. As I recall it, there was a right quadrantanopsia; yet this tumor was on the right side of the cerebral hemisphere.

With respect to the question of the tumor being in the depths of the cortex, I recall Dr. Riggs showing us a number of cases in which the meningioma was deep within the substance of the brain, but I do not recall any cystic formation in them.

Dr. Gabriel Schwartz: I want to ask Dr. Grant whether the cyst might be due to vascular occlusion in this area of the brain. I think that must be considered a possibility. I wonder whether he had any feeling that the cyst might be a necrotic walled area.

Dr. Henry Wycis: Two years ago, before this society, Dr. Scott presented the case of a child who had a glioma of the left frontal lobe, with a Parkinsonian-like tremor. After the tumor was removed, the Parkinsonian-like tremor disappeared. Dr. Scott believed that this glioma encroached on the basal ganglia.

Dr. Francis C. Grant: The chronology of events in this case is interesting. At 13, this man had a paralyzing epidemic encephalitis. At 30 he had a blow on the head, and at 35 he began to be nervous and irritable. It is probable that at 13 he had an encephalitis which produced a lesion in the right cerebral cortex. Then he had a blow on the head, which may well have increased the damage about this preexisting lesion. Lastly, he had a tumor, which in all probability lay behind and medial to the original lesion. I think that he might have had this cyst as a result of the original lesion whether he had had the tumor or not. I do not believe that this meningioma can be said to be deep in the brain. It was attached to the falx over an area at least 2 cm. in diameter and extended laterally from this attachment to the falx into the right cerebral hemisphere in the midparietal area. This case presented such a unique combination of circumstances—encephalitis, injury and tumor, all in about the same area of the brain—that I thought it worth reporting.

Seizures Involving the Second Sensory Area. Dr. George D. Gammon, Dr. Francis C. Grant and Dr. Dora Papara (by invitation).

Adrian's discovery of a second sensory area in the frontal and parietal operculum and the confirmation and extension of the mass, reported by Woolsey and Bard, show representation of the same and the opposite side of the body in the snout area. This sensory distribution would appear to provide a localization for the attacks in two patients in whom sensory seizures began in the hand and then spread to involve the mouth or nose and the upper and lower lips on both sides. One of these had a tumor in the parietal region; the other had a disorder diagnosed as migraine.

Penfield's work in man and that of Sugar, Chusid and French suggest that the region has also motor function, sometimes homolateral. Two cases of tumor of the temporal lobe were described in which homolateral attacks were observed—in one case motor and in the other sensory. In both, focal discharge was found in the region of the second sensory-motor area.

DISCUSSION

DR. FRANCIS C. GRANT: I was interested in Dr. Gammon's point that ipsilateral convulsions can occur from a lesion in the cerebral cortex. Such an unusual situation would have to be documented to be authentic. On the other hand, I have no doubt that the situation developed as described.

Recently, Dr. William Sweet, in Boston, who stimulated the anterolateral columns of the spinal cord at the same time that a chordotomy was done, found that occasionally the spinothalamic tract apparently does not decussate. In one case he noted that when the right spinothalamic tract was stimulated pain was referred to the lower extremity on the right side. In another case stimulation of one spinothalamic tract was followed by pain in both lower extremities. Again, a case was reported in which the patient had pain in the left leg. A right spinothalamic section had little or no effect on the pain. Sweet proved that stimulation of the left spinothalamic tract produced pain on the left side and section of that tract relieved the pain on that side.

There must be variations and deviations, therefore, in these sensory pathways. If there are deviations in sensory pathways, there is no reason that there should not be deviations in motor pathways, and this may well account for the atypical situation that Dr. Gammon has described.

DR. AXEL OLSEN: I have not seen any case of ipsilateral convulsions. I agree with what was said. This secondary sensory-motor cortex should be investigated for the explanation of some of these obscure seizures. As more and more epileptic patients are operated on, and these areas of the cortex are excised, we shall learn some instructive things about the cortex and its manner of functioning.

DR. ALEXANDER SILVERSTEIN: Dr. Gammon and his associates have presented a most interesting and instructive paper on the function of the sensory sortex. In 1931, I presented before this society a case of tumor of the parietal lobe in which sensory and motor Jacksonian seizures occurred, at first involving the tongue, pharynx, larynx and face and later spreading to include the thumb and index finger. An early and striking finding was atrophy of the muscles of the left upper limb, a sign which I then emphasized as an important indication of involvement of the post-Rolandic region and of the parietal lobe. One of the unusual features in my case was the fact that the sensory Jacksonian seizures at times affected simultaneously the right and left hands. The motor Jacksonian seizures, in addition to causing twitching of the left side of the face, occasionally involved the upper part of the right side of the face. A search of the literature at that time disclosed only one human case of a bilateral pattern of a Jacksonian sensory seizures. However, in animal experiments, Dusser de Barenne showed that stimulation of an area in the sensory cortex with strychnine resulted in a bilateral effect on the two sides of the body, more pronounced on the contralateral side.

DR. HENRY WYCIS: Apropos of what Dr. Grant has said, Dr. Sweet described another interesting case. When he stimulated the spinothalamic tract, the patient had pain in both legs. The spinothalamic tract was sectioned contralaterally, and the pain persisted on the affected side despite a satisfactory sensory loss. He had the courage to do an ipsilateral chordotomy. After the second chordotomy the patient was relieved. In a case reported by French unilateral chordotomy was followed by ipsilateral sensory loss. There are cases in which hemispherectomy for glioma was followed by complete loss of sensation on the opposite side of the body, except in the face.

DR. GEORGE D. GAMMON: Dusser de Barenne found, by stimulation of the cortex with strychnine, a bilateral representation from the postcentral convolution. He could differentiate an arm, a leg and a face area. This observation is interesting, for, according to von Bonin, there is no commissural connection between the postcentral convolutions of the two sides via the corpus callosum. Furthermore, Woolsey found strictly unilateral responses in the postcentral convolutions. How to explain this divergence in the light of anatomical terms is not clear.

News and Comment

CHARLES C. BURLINGAME, M.D.

In their annual report, the board of directors of the Institute of Living noted that Dr. Charles C. Burlingame, psychiatrist in chief of the Institute from 1931 until his death, in England, last July, had found the Institute beset by many difficulties. "Nothing daunted him in facing the ever-changing progress of scientific treatment of the mentally ill." He transformed the hospital into the progressive institution of today, inaugurating a widely copied educational therapy program and thus "evidencing his faith that a mental hospital should not be aimed at furnishing a withdrawal from the world but should be dedicated to the re-education of its patients so that they might return to performing useful services to society according to their individual capacities."

ANNUAL MEETING OF AMERICAN NEUROLOGICAL ASSOCIATION

The Seventy-Sixth Annual Meeting of the American Neurological Association will be held at the Hotel Claridge, Atlantic City, N. J., from June 18 to 20, 1951. Communications may be addressed to the secretary, H. Houston Merritt, M.D., 710 West One Hundred and Sixty-Eighth Street, New York.

Obituaries

LAWRENCE RAYMOND MORRISON, M.D.
1897-1950

Ray Morrison was a sensitive, brilliant man with great courage and singleness of purpose. He wanted to be a neuropathologist; for this he trained himself thoroughly, and at this he worked throughout all his too-short professional years. The tragedy of his untimely death at the age of 53, in the midst of his most creative work, was unexpected and sudden. It was the end of his 20 year fight against tuberculosis. Stricken in 1931, just as he was getting into his stride as an investigator, he was unable to work for four years and underwent many thoracic operations. In 1935 he was able to take up part time teaching and research, but this was interrupted by much illness and more surgical treatment. He gradually gained strength; so from 1940 until his death he was able to work full time as an experimental neuropathologist at the Massachusetts General Hospital and teach neuropathology at the Harvard Medical School. Only those who worked with him knew how his marvelous enthusiasm for his work lifted him above pain and fatigue. His shy manner and dry humor were sometimes surprising opposites in his complex character. He worked in a special field but easily learned new methods from others. Little went on in the hospital and the world about him that he did not see. He enjoyed reading and art and could draw well. He was married to Hazel Simmons in 1929. A daughter was born in 1930 and a son in 1931. They lived in Brookline and spent their summers at Sheffield, in the Berkshire Hills.

Morrison was born in West Springfield, Mass., in 1897. He attended Tufts College (1920) and then Tufts College Medical School, where he graduated as Doctor of Medicine in 1924. He had a general internship at St. Luke's Hospital in New Bedford, and a year of psychiatry at the Danvers State Hospital. He then began his special training by working for six months under Barrett at the Psychopathic Hospital in Ann Arbor, Mich. In 1926-1927 he spent a year in Ferraro's laboratory at the Psychiatric Institute in New York city. The following year he held the Laan fellowship at the University of Utrecht in the Netherlands. Here he worked on anatomy under Winkler and pathology under Rademaker. This was a great stimulus, and he always spoke with happiness of the experience and with admiration for Professor Winkler. Returning to America in 1929, he took up his life's work, teaching neuropathology at the Harvard Medical School and running the histological laboratory of the neurological unit at the Boston City Hospital, where he became neuropathologist in 1930. A year later came his illness. On returning to work, he transferred his research to the laboratories of the Massachusetts General Hospital, where he carried on his investigations up to the time of his death. From 1929 to 1941 he was an assistant in neuropathology at the Harvard Medical School. In 1941 he was advanced to instructor and in 1948 to associate. Although his bibliography consists of only 14 titles, it is remarkable in that it shows the consistency of his effort to do fundamental research along experimental lines. It also shows the long range manner in which he outlined problems and carried them through. Each of his publications is a real monograph and is of a high standard of excellence. He never published anything trivial or "preliminary."

LAWRENCE RAYMOND MORRISON, M.D.
1897-1950

His first paper [1] was a description of the work done with Ferraro in New York during the years 1926 to 1927. It was an investigation of the effect of illuminating gas on the cells of the central nervous system, and it turned his interest toward experimental work and the effects of anoxia, trends which strongly influenced his later investigations. The following year he was enjoying his *Wanderjahr* in the Netherlands, and in Winkler's laboratory produced an important anatomical study [2] showing a tract from the pallidum to the reticular formation of the brain stem. His interest in the demyelinating disorders became apparent shortly after his return to Boston, in his work with Putnam on experimental sclerotic plaques,[3] his study of the effect of electric shock on the brain [4] and, especially, his important description of the role of the oligodendroglia in myelogenesis.[5] It was just as he was developing new methods for this research that he fell ill.

Returning to research just before the war, his interest in the effects of oxygen deprivation on the brain led to his being chosen to investigate for the Navy the cerebral effects of anoxia in a quantitative way. Qualitative work had been done before, but he first showed what sort of lesions appeared, and where, after known amounts of asphyxia for measured periods of time. It was a laborious investigation, including physiological and chemical determinations, along with histopathological observations.[6]

The last five years of his life Morrison devoted to two related lines of research, the investigation of the neuropathology of rheumatoid arthritis and the effects on the nervous system of allergic reactions. He showed that a disseminated encephalomyelitis could be produced in animals by the use of homologous antigens [7] and was tracking down the part played by enzymes in such phenomena.[8] His latest papers [9] were on the immunological aspects of encephalomyelitis. This work represents an original and hopeful attack on the obscure problem of the etiology of such diseases as multiple sclerosis.

---

1. Ferraro, A., and Morrison, L. R.: Illuminating Gas Poisoning: An Experimental Histopathological Study, Psychiat. Quart. **2**:506, 1928.

2. Morrison, L. R.: Anatomical Studies of the Central Nervous System of Dogs Without Forebrain or Cerebellum, Haarlem, Netherlands, de Erven F. Bohn, 1929.

3. Putnam, T. J.; McKenna, J., and Morrison, L. R.: Studies in Multiple Sclerosis: Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931; Experimental Demyelination, Tr. Am. Neurol. A. **57**:451, 1931.

4. Morrison, L. R.; Weeks, A., and Cobb, S.: Histopathology of Different Types of Electric Shock on Mammalian Brains, J. Indust. Hyg. **12**:324, 1930.

5. Morrison, L. R.: Role of Oligodrendroglia in Myelinogenesis, Tr. Am. Neurol. A. **57**: 444, 1931.

6. Morrison, L. R.: Histopathologic Effect of Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **55**:1 (Jan.) 1946.

7. Morrison, L. R.: Disseminated Encephalomyelitis Experimentally Produced by Use of Homologous Antigen, Arch. Neurol. & Psychiat. **62**:688 (Nov.) 1949.

8. Morrison, L. R., and Zamecnik, P. C.: Experimental Demyelination by Means of Enzymes, Especially the Alpha Toxin of Clostridium Welchii, Arch. Neurol. & Psychiat. **63**:367 (March) 1950.

9. Waksman, B. H., and Morrison, L. R.: Tuberculin Type Sensitivity to Spinal Cord Antigen in Rabbits with Isoallergic Encephalomyelitis, J. Immunol. **66**:421, 1951. Freund, J.; Lipton, M. M., and Morrison, L. R.: Demyelination in the Guinea Pig in Chronic Allergic Encephalomyelitis Produced by Injecting Guinea Pig Brain in Oil Emulsion Containing a Variant of Mycobacterium Butyricum, Arch. Path. **50**:108 (July) 1950.

In relation to arthritis, he worked for years as neuropathological advisor to Walter Bauer's laboratory group. This resulted in a general paper [10] outlining the problem in 1947. To evaluate the postmortem changes found, it was necessary to know just what changes occurred in the spinal cord with advancing age. Morrison therefore prepared as controls specimens from 50 spinal cords of persons aged from 10 to 90 and described and photographed the changes in nerve cell, axon, myelin, glia and connective tissue. This makes a unique book, which will soon be brought to completion.[11] In the postmortem study of many arthritic patients he had found nodular inflammatory lesions in the interstitial tissues of nerve and muscle. This material is also being prepared for publication.[12] In addition, he was making preparations of synovial cells stained by DaFario's method to see whether there was any relation between the secretion of synovial tissue and the Golgi apparatus.[13]

He died in the midst of all this activity, still enthusiastic and always pushing himself to the limit of his strength. His loss is a very real one to science. His friends and colleagues have lost a companion of rare quality.

STANLEY COBB, M.D.

---

10. Morrison, L. R.; Short, C. L.; Ludwig, A. O., and Schwab, R. S.: The Neuromuscular System in Rheumatoid Arthritis: Electromyographic and Histological Observations, Am. J. M. Sc. **214**:33, 1947.

11. Morrison, L. R.: Alterations in the Spinal Cord with Advancing Age, to be published.

12. Morrison, L. R.: Lesions of Nerve and Muscle in Rheumatoid Arthritis, to be published.

13. Morrison, L. R.: The Golgi Apparatus and Synovial Activity, to be published.

Book Reviews

The Neural Crest: Its Properties and Derivatives in the Light of Experimental Research. By Sven Hörstadius. Pp. 111, with 46 figures. Price, $3. Oxford University Press, 114 5th Ave., New York 11, 1950.

The neural crest has long been recognized as the source of the spinal and cranial nerve ganglia and has also been implicated in the development of the leptomeninges. It remained, however, for the experimental embryologist to reveal how this early structure is important also for the development of the cranial bones, the teeth and the whole pigmentary system of the body. Hörstadius, who is professor of zoology at the University of Uppsala, reviews the whole subject in a series of special lectures at University of London, and shows how the intricate and exacting methods of excising, rotating, transplanting and interchanging the neural crest at early stages of development can bring about peculiarities in later morphology, and thus reveal the part played by this interesting structure. Vital staining with nile blue sulfate and neural red in alternating bands along the developing neural crest give one picture. Interchanging the neural crests of two species whose cells differ as to size, nuclear value and pigmentary characteristics give another. By timing the experiments, the migration of the chromatoblasts can be followed in their migration from the neural crest to various parts of the body.

There is much more in this small monograph, together with redrawn figures from various previous authors. It is illuminating to find out how actively this field is being developed. The ingenuity of the experiments, as well as the passionate devotion of the workers in the field, is encouraging. The next step in the development of the subject will probably be the "tagging" of transplants with radioactive tracers.

Hypnotherapy of War Neuroses: A Clinical Psychologist's Casebook. By John G. Watkins, Ph.D. Price, $5. Pp. 384. The Ronald Press Co., 15 E. 26th St., New York 10, 1949.

This is a report of psychotherapy done by the author while working in the neuropsychiatric division of an Army convalescent hospital during World War II. The men whose treatment is described in the case studies were combat veterans who broke under the stress of war and needed individual therapy. They received this treatment in a "special treatment company." Hypnosis was used as an integral part of their treatment. The cases were selected to illustrate the different forms which war neuroses may take and the evaluation of therapeutic "attacks" which were necessary to bring about improvement. The case reports are presented for their interest to other clinical psychologists and to the professional student of hypnotherapy. The author seems to have stopped studying Freud's work with "Studies in Hysteria." The book proves what long has been known, that neurotic sickness which is chiefly based on the mechanism of repression can be symptomatically cured by hypnosis.

Speaking of Man. By Abraham Myerson, M.D. Price, $3.00. Pp. 279. Alfred A. Knopf, Inc., 501 Madison Ave., New York 22, 1950.

An autobiography is always greeted with expectations, especially when written by a contemporary psychiatrist. Myerson's autobiography is not an exception and, in spite of its unfinished quality, not a disappointment. The book is not limited strictly to autobiographical details but contains "germs of hope and a sketch of embryonic possibilities for the real living for man" as Myerson saw it. Of special interest are the excerpts from the correspondence between Myerson and his publisher Knopf regarding the growth of this book. A biographical note, written by Mildred N. Myerson, increases the value of the book considerably.

North Shore Health Resort

on the shores of Lake Michigan

WINNETKA, ILLINOIS

NERVOUS and MENTAL DISORDERS
ALCOHOLISM and DRUG ADDICTION

Modern Methods of Treatment

MODERATE RATES

Established 1901
Licensed by State of Illinois

Fully Approved by the
American College of Surgeons

SAMUEL LIEBMAN, M.S., M.D.
Medical Director

225 Sheridan Road **Winnetka 6-0211**

Founded 1879

RING SANATORIUM

Eight miles from Boston at an elevation of 400 feet

For the study, care and treatment of emotional, mental, personality and habit disorders.

All recognized psychiatric therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric or neurological supervision.

BENJAMIN SIMON, M.D., *Director*

CHARLES E. WHITE, M.D., LOUIS BRENNER, M.D.
FRED E. LAWRENCE, M.D.
Associates

Consultants in all Specialties

Arlington Heights, Massachusetts
Telephone AR 5-0081

Francis W. Russell
Executive Secretary

"Beverly Farm"

INCORPORATED
Founded 1897
INCORPORATED 1922

11 buildings
220 acres of land
300 feet above
Mississippi River

HOME AND SCHOOL FOR
Nervous and Backward Children

Can accommodate 200 children, with contemplated educational improvements for a larger number. Can accept some suitable case for life.

Address all communications to **DR. GROVES B. SMITH, SUPERINTENDENT**
"Beverly Farm" **GODFREY, MADISON COUNTY, ILLINOIS**

BROOKLEA FARM

A convalescent home to provide care and treatment for patients convalescing from physical illness or suffering from mild personality disorders. Medical treatment is provided by the consulting and referring staff. Psychotherapy by resident and associated psychiatrists. Nursing and dietetic needs are met by trained personnel.

Brooklea Farm is an 80-acre country estate which includes a dairy, poultry farm, vegetable and flower gardens, orchards, nursery and greenhouse and many acres under cultivation.

Patients may stroll through open fields, along shaded lanes or beside Blind Brook which flows through a wooded section of the estate. They may engage in farm activities, work in the gardens, play tennis, croquet or golf, or participate in various forms of occupational therapy.

The privileges of a private home are afforded to visitors. Relatives and friends may live at Brooklea when this is an aid to treatment.

BROOKLEA FARM

Rt. 120A, King St., Port Chester, N. Y. Tel.: Port Chester 5-0333
New York office: 11 East 71st St. Tel.: Trafalgar 9-2660

GEORGE W. HENRY, M.D.
Psychiatrist-in-charge

Your "experience exchange" in the field of Skin Diseases and Syphilis—A valuable guide in your Practice—

A. M. A. Archives of DERMATOLOGY and SYPHILOLOGY

SIGNIFICANT DEVELOPMENTS reported monthly to the specialist and the physician in general practice. From hospitals, clinics and government treatment centers here and abroad, A. M. A. Archives of DERMATOLOGY and SYPHILOLOGY gathers news of current trends in treatment and diagnosis, group case studies, clinical notes and comments on cutaneous conditions and syphilis.

Well illustrated.

Ably edited.

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago 10, Illinois.

Please Begin My Subscription to A. M. A. Archives of DERMATOLOGY and SYPHILOLOGY with the Next Issue.

.....M.D.
.....STREET
.....CITY AND STATE

$12.00 YEARLY
$13.50 FOREIGN $12.40 CANADIAN

BROOK HAVEN MANOR

Here the mentally and emotionally sick patient will find all the traditional charm of a Southern Manor House . . . a bright and friendly world of smart decor, pleasing diversion and memorable cuisine . . . blended with individualized methods of treatment.

NEWDIGATE M. OWENSBY, M.D.
Psychiatrist in Chief

Brook Haven Manor
Stone Mountain, Ga.

THE LIVERMORE SANITARIUM

LIVERMORE, CALIFORNIA
San Francisco Office - 450 Sutter Street

For the Treatment of Nervous and Mental Diseases

THE HYDROPATHIC DEPARTMENT, for nervous and general patients; the Cottage Department, for mental patients. FEATURES: near Oakland and San Francisco; ideal climate; large beautiful grounds; hydrotherapy, athletic and occupational departments; clinical laboratory; large trained nursing force. Rates include these facilities: Room, suitable diet, and general nursing care. Booklet on request.

O. B. JENSEN, M.D., Superintendent and Medical Director **Consulting—J. W. Robertson, M.D.**

Child Health

Bad Habits in Good Babies. Herman M. Jahr. **16 pages.** 15 cents.

What Does Your Baby Put in His Mouth? Chevalier Jackson and Chevalier L. Jackson. Tells how to prevent accidents from choking and what to do if they happen. 24 pages. 10 cents.

Keeping Your Baby Well. 22 pages. 10 cents.

The Case of the Crying Baby. Herman M. Jahr. 4 pages. 10 cents.

What to Do About Thumb Sucking. William I. Fishbein. 6 pages. 10 cents.

Lefthandedness. Paul Popenoe. 8 pages. 10 cents.

Adoption. W. Allison Davis and Theo Carlson. An understanding discussion of the best ways to adopt children and rear them. 12 pages. 15 cents.

Protecting Your Child from Allergy. William Gayle Roberts. 8 pages. 10 cents.

The Facts About Sex. Audrey McKeever. 16 pages. 15 cents.

Please remit with order

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St. • Chicago 10

CLEARVIEW

ON THE KRATZVILLE ROAD
EVANSVILLE, INDIANA
TELEPHONE 5-6181

A PRIVATE HOSPITAL FOR THE TREATMENT OF PATIENTS SUFFERING FROM NERVOUS AND MENTAL ILLNESS, ALCOHOLISM AND DRUG ADDICTION.

SEPARATE BUILDINGS FOR DISTURBED AND CONVALESCENT PATIENTS.

Equipped for Surgery

ELECTROENCEPHALOGRAPH
CLINICAL LABORATORY
ELECTROCARDIOGRAPH
STEREOSCOPIC X-RAY
BASAL METABOLISM
HYDROTHERAPY

Albert J. Crevello, M.D.
Diplomate, American Board of Psychiatry & Neurology, Inc.
MEDICAL DIRECTOR

"Twenty Minutes from Times Square"

RIVER CREST SANITARIUM

ASTORIA, L. I., NEW YORK CITY

A MODERN SANITARIUM for NERVOUS and MENTAL patients with special facilities for ALCOHOLIC cases. Physicians are invited to cooperate in the treatment of patients recommended.

All Types of Recognized Therapy

REASONABLE RATES

Exceptionally located in a large beautiful private park EASILY ACCESSIBLE BY ALL CITY RAPID TRANSIT LINES.

Six attractive buildings, with complete classification.

Information on Request

LAYMAN R. HARRISON, M.D., Physician in Charge
JOHN CRAMER KINDRED, M.D., Consultant

Long Established and Licensed—On A. M. A. Registered Hospital List

BELLE MEAD SANATORIUM

BELLE MEAD, N. J.

For NERVOUS, MENTAL and ALCOHOLIC patients and ELDERLY people.

FOUR ATTRACTIVE MODERN BUILDINGS with PROPER CLASSIFICATION

Scientific Treatment—Efficient Medical and Nursing Staff
Occupational Therapy

BOOKLET SENT ON REQUEST

Located on 300 ACRE MODEL FARM, at the foot of the WATCHUNG MOUNTAINS—1¼ hours from NEW YORK or PHILADELPHIA, via Reading R. R.

JOHN CRAMER KINDRED, M.D., Consultant

Telephones { Belle Mead 21 / New York—AStoria 8-0820

Long Established and Licensed—On A. M. A. Registered Hospital List

For a Better Understanding of Nervous and Mental Diseases

A. M. A. Archives of NEUROLOGY and PSYCHIATRY gives practical assistance to those readers who would keep well informed about the rapid progress in these fields. It presents original articles, clinical notes, special articles, society transactions and book reviews and book notices. Each issue includes a large number of brief digests from current medical literature which present significant findings of eminent neurologists and psychiatrists throughout the world. Well illustrated. Issued monthly. Averages about 2730 pages annually. Price, $12.00 a year. Canada, $12.40. Foreign, $13.50.

AMERICAN MEDICAL ASSOCIATION **535 N. Dearborn St., Chicago 10**

ADAMS HOUSE

Established 1877

☆

A non-commitment sanitarium and clinic, club-like in physical setting and atmosphere, applying re-educational psychotherapeutic methods in the study and treatment of the **psychoneuroses** exclusively.

Located in suburban Boston contiguous to and overlooking the Arnold Arboretum

☆

James Martin Woodall, M.D., Medical Director

990 CENTRE STREET, BOSTON,
Jamaica Plain, MASS.

"NORWAYS"

(Non Profit)

STERNE MEMORIAL HOSPITAL

Indianapolis, Indiana

Established 1898 for

NEUROPSYCHIATRIC DISORDERS

DIPLOMATES OF AMERICAN BOARD OF:
PSYCHIATRY AND NEUROLOGY

D. BROWN, M.D. — M. DE ARMOND, M.D.
J. H. GRIEST, M.D. — C. K. HEPBURN, M.D.
E. W. MERICLE, M.D. — L. W. NIE, M.D.
G. RADER, M.D. — P. B. REED, M.D.
D. SCHUSTER, M.D. — E. R. SMITH, M.D.

INTERNAL MEDICINE

WENDELL A. SHULLENBERGER, M.D.

PHONE AT. 1551 — 1800 E. 10th ST.

CLINICAL STAFF

•

MEDICAL STAFF OF PENNSYLVANIA

Leslie R. Angus, M.D.
Robert Devereux, M.D.
Ruth E. Duffy, M.D.
Herbert H. Herskovitz, M.D.
Ruth Stephenson, M.D.

•

PSYCHOLOGICAL STAFF OF PENNSYLVANIA

Edgar A. Doll, Ph.D.
Director of Research
Michael B. Dunn, A.M.
Robert G. Ferguson, A.M.
Edward L. French, Ph.D.
Mary J. Pawling, A.M.

MATURITY through Education with Therapy

NEVER before has the need been so great for maturity in our adult population . . . for clear, objective thinking and a realistic facing-up to problems—both personal and social. The emotionally disturbed child stands a poor chance of becoming a mature and valuable citizen unless he has specialized help . . . understanding guidance and encouragement in solving the problems commensurate to his age.

When, in your practice, you feel that a school-age patient needs specialized education and guidance, we invite you to let us evaluate the potential outcome. When the intelligence is normal, but emotional disturbances block the ability to learn, our experienced staff will carefully study the details and offer a considered report.

Please address your inquiries to
JOHN M. BARCLAY, *Registrar*

DEVEREUX FOUNDATION
CALIFORNIA . . . PENNSYLVANIA

Devereux Schools

HELENA T. DEVEREUX, *Director*

SANTA BARBARA, CALIFORNIA — DEVON, PENNSYLVANIA

THE E & J RESUSCITATOR-ASPIRATOR-INHALATOR

SHOCK THERAPY IN

. . . the immediate availability of a modern E & J precision Resuscitator, ready instantly to assume the complete breathing function for the patient and to continue it until normal breathing is restored, accomplishes the dual purpose of:

1. Increased skill born of greater assurance.
2. Increased protection for the patient.

You can best appraise the effectiveness of the E & J Resuscitator in your therapeutic work by seeing it in actual operation. A thorough demonstration will gladly be arranged at your convenience, without obligation. Please write to . . .

E & J MANUFACTURING CO.
DEPT. 514-7, GLENDALE 1, CALIFORNIA

it would take a fair-sized apartment building

to house all of the patients who represent each of the many conditions for which short-acting NEMBUTAL *is effective*

TWENTY-ONE YEARS of clinical use, 554 references in the literature, 44 effective uses—these are some of the factors responsible for the steadily growing popularity of short-acting NEMBUTAL with the medical profession.

Short-acting NEMBUTAL can provide any desired degree of cerebral depression—from mild sedation to deep hypnosis. Small dosage—only about *one-half* that of many other barbiturates—means shorter duration of effect, wide margin of safety, and less possibility of barbiturate hangover. Keep NEMBUTAL in mind for any short-acting sedative need.

Abbott

in equal oral doses, no other barbiturate combines QUICKER, BRIEFER, MORE PROFOUND EFFECT than...

NEMBUTAL®
(PENTOBARBITAL, ABBOTT)